

- Cardiology (290)
- Clinical haematology/oncology (171)
- Clinical pharmacology and toxicology (273)
- Clinical sciences (410)

2600 MCQ with Illustrated Answer

Full Topics Note

14 Chapter

Clinical sciences

P. M MCQ Bank 2017

- Infectious diseases and STIs (212)

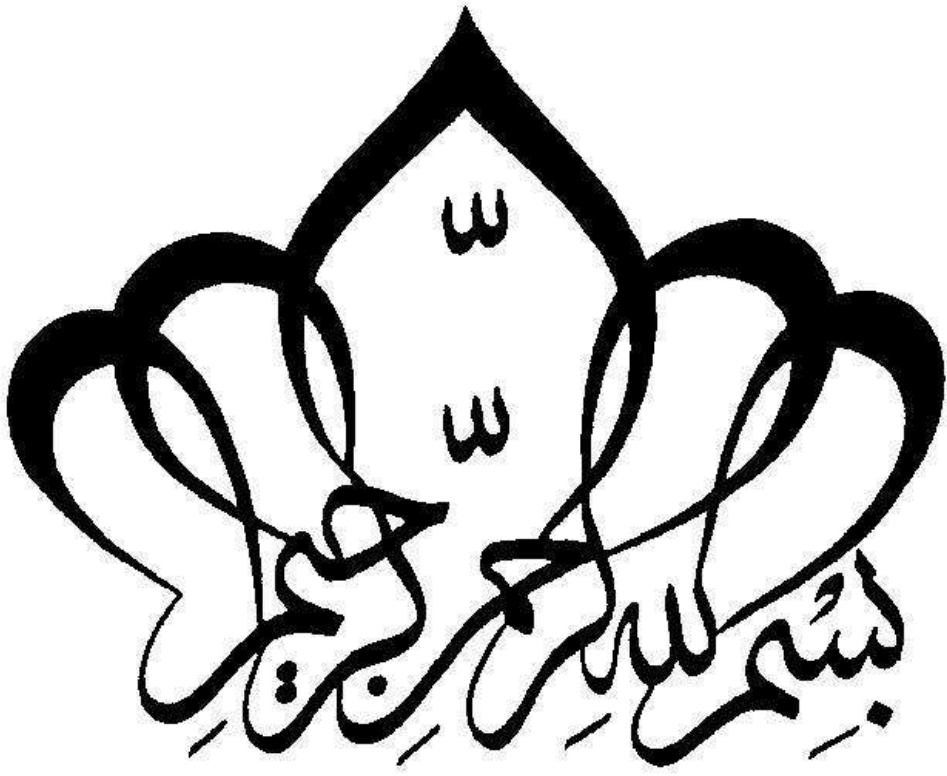
-Neurology (247)

- Respiratory medicine (162)



VISIT...

LANZAROTE
Caliente.COM



قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا
۞ إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

إهداء

للكل آية من كتاب الله حفظناها ولكل معلومة قرأناها ونسيناها لعل الله يحمينا من النسيان ويروها إلينا
للكل شخص وعونا له في ظهر الغيب لعل الله أن يستجيب وعائنا
للكل مريض قرأله ما أله لعل الله يشفيه ويعير إليه صحته وعافيته
للكل لحظة تألم بها أحببنا لعل الله لا يريهم الألم ولا يضييهم مرة أخرى
للكل موقف اجتجت به عينا فلم تلباني لعل الله لا يضرنى بهما في حياتي
للكل حالم صاحب أهراء ومباوى لعل الله يحقق له مقاصده حتى يرضيه ويرضى عنه
للكل مجتهد لعل الله يجعل له من التوفيق أوفر حظ ونصيب ويهون له الأسباب كلها من حيث لا يدري من غير ضراء مضرة ولا فتنة مضلة
للكل من فقر شيئا في الحياة لعل الله يعيره إليه أو يعوضه بما يسعده
للكل شخص ابتعدنا عنه لعل الله يجمعه بمن هم أفضل منا
وأخيرا وليس آخرا لأهلنا لعل الله يجعلها لهم صرقة جارية ترو إليهم قليلا من فضلهم علينا وتكون سببا يلم شملنا تحت سقف واحد بعد أن
هجرتنا الحروب والمصائب

يقول أحد الصالحين

إِذَا رَأَيْتَ أَنَّ اللَّهَ وَفَقَكَ لِإِخْوَةِ تَعْيْنِكَ عَلَى الْخَيْرِ.. فَأَعْلَمْ أَنَّ اللَّهَ يَرِيدُ بِكَ خَيْرًا !! وَإِذَا وَفَقَكَ اللَّهَ لِلدُّعَاءِ.. فَأَعْلَمْ أَنَّ اللَّهَ يَرِيدُ أَنْ يُعْطِيَكَ !! وَإِذَا
وَفَقَكَ لِقَضَاءِ حَوَائِجِ النَّاسِ فَأَعْلَمْ أَنَّ لَكَ يَتَخَلَّى عَنْكَ !! وَإِذَا وَفَقَكَ اللَّهَ لِذِكْرِهِ.. فَأَعْلَمْ أَنَّكَ مُحِبٌّ !!.. وَإِذَا أَحْبَبَّكَ أَحَدٌ.. وَنَصَرَكَ.. وَأَيَّرَكَ..
وَأُسْتَجَابَ لِدُعَائِكَ !!

This issue of **MRCPPART1 MADE EASY 2017** contains the following:

- Full topic note.
- Around 2600 MCQs from **PM 2017 BANK** covering 14 chapter in internal medicine
- External links for the related guidelines (such as NICE, SIGN, RCP ...etc).
- Comments with illustrative pictures and links to external media.
- Most Recommended QBank for MRCP Part 1, Arab Board, Jordanian Board and other internal medicine assessment exams.

Please Note that

Each chapter begins with notes section. These notes are repeated under the Questions in the website. In these collections the notes are not repeated under each question except in some to avoid unnecessary repetition. For clarity and convenience the title of the related note is only mentioned after the comments in case the reader want to refer back to the respective note in the notes section.

The illustration below is to show and Example

☐	Minimal change disease
☐	Post-streptococcal glomerulonephritis
☐	Goodpasture's syndrome

Goodpasture's syndrome

- IgG deposits on renal biopsy
- anti-GBM antibodies

• These changes are characteristic of Goodpasture's syndrome.

[Discuss and give feedback](#)

Goodpasture's syndrome 

Comment of the Q

title of the note in case the reader want to refer back to the notes sections

MRCPPART1 MADE EASY 2017

Chapter	Number of Q
Cardiology	292
Clinical haematology/oncology	171
Endocrinology	174
Gastroenterology	183
Infectious diseases and STIs	212
Nephrology	104
Neurology	247
Respiratory medicine	162
Rheumatology	134
Clinical pharmacology and toxicology	273
Clinical sciences	410
Dermatology	131
Ophthalmology	56
Psychiatry	59

إعداد وتنسيق

M. HABAYEB

**Msc Internal. Medicine
Cairo University**

&

A. MURAD

لا تنسونا من صالح دعائكم

ما كان من خطأ فمن أنفسنا وما كان من توفيق فمن الله

تم بحمد الله وتوفيقه ومنه

جعل الله عملنا متقبلاً خالصاً لوجهه الكريم

Reference ranges

Reference ranges vary according to individual labs. All values are for adults unless otherwise stated

Full blood count

Haemoglobin	Men: 13.5-18 g/dl Women: 11.5-16 g/dl
Mean cell volume	82-100 fl
Platelets	150-400 * 10 ⁹ /l
White blood cells	4-11 * 10 ⁹ /l

Urea and electrolytes

Sodium	135-145 mmol/l
Potassium	3.5 - 5.0 mmol/l
Urea	2.0-7 mmol/l
Creatinine	55-120 umol/l
Bicarbonate	22-28 mmol/l
Chloride	95-105 mmol/l

Liver function tests

Bilirubin	3-17 umol/l
Alanine transferase (ALT)	3-40 iu/l
Aspartate transaminase (AST)	3-30 iu/l
Alkaline phosphatase (ALP)	30-100 umol/l
Gamma glutamyl transferase (γGT)	8-60 u/l
Albumin	35-50 g/l
Total protein	60-80 g/l

Other haematology

Erythrocyte sedimentation rate (ESR)	Men: < (age / 2) mm/hr Women: < ((age + 10) / 2) mm/hr
Prothrombin time (PT)	10-14 secs

Activated partial thromboplastin time (APTT)	25-35 secs
Ferritin	20-230 ng/ml
Vitamin B12	200-900 ng/l
Folate	3.0 nmol/l
Reticulocytes	0.5-1.5%
D-Dimer	< 400 ng/ml

Other biochemistry

Calcium	2.1-2.6 mmol/l
Phosphate	0.8-1.4 mmol/l
CRP	< 10 mg/l
Thyroid stimulating hormone (TSH)	0.5-5.5 mu/l
Free thyroxine (T4)	9-18 pmol/l
Total thyroxine (T4)	70-140 nmol/l
Amylase	70-300 u/l
Uric acid	0.18-0.48 mmol/l

Arterial blood gases

pH	7.35 - 7.45
pCO2	4.5 - 6.0 kPa
pO2	10 - 14 kPa

Lipids

Desirable lipid values depend on other risk factors for cardiovascular disease, below is just a guide:

Total cholesterol	< 5 mmol/l
Triglycerides	< 2 mmol/l
HDL cholesterol	> 1 mmol/l
LDL cholesterol	< 3 mmol/l

Achondroplasia	Notes
Acute intermittent porphyria	Notes
Acute liver failure	Notes
Acute phase proteins	Notes
Adrenal medulla	Notes
Adrenoceptor agonists	Notes
Adrenoceptor antagonists	Notes
Adrenoceptors	Notes
Altitude related disorders	Notes
Anaphylaxis	Notes
ANCA	Notes
Angiodysplasia	Notes
Anion gap	Notes
Antidiuretic hormone	Notes
Antiviral agents	Notes
Arterial blood gas interpretation	Notes
Atherosclerosis	Notes
Atrial natriuretic peptide	Notes
Atropine	Notes
Autosomal dominant	Notes
Autosomal dominant conditions	Notes
Autosomal recessive	Notes
Autosomal recessive conditions	Notes
Avascular necrosis	Notes
B-type natriuretic peptide	Notes
Calcium metabolism	Notes
Cardiac action potential	Notes
Cardiac imaging: non-invasive techniques excluding echocardiography	Notes
Cardiovascular physiology	Notes
Cell cycle	Notes
Cell division	Notes
Cell organelles	Notes
Cell surface proteins	Notes
Cervical cancer	Notes
Chronic kidney disease: bone disease	Notes
Clinical trial: phases	Notes
Cocaine	Notes
Colorectal cancer: referral guidelines	Notes
Common peroneal nerve lesion	Notes
Complement deficiencies	Notes
Complex regional pain syndrome	Notes
Confidence interval and standard error of the mean	Notes
COPD: causes	Notes
Cystic fibrosis	Notes
Cystinuria	Notes

DiGeorge syndrome	Notes
Down's syndrome: epidemiology and genetics	Notes
Endothelin	Notes
Energy from food	Notes
Epidermis	Notes
Erythrocyte sedimentation rate (ESR)	Notes
Folate metabolism	Notes
Food energy	Notes
Foramina of the skull	Notes
Fourth nerve palsy	Notes
Fragile X	Notes
Funnel plot	Notes
Galactosaemia	Notes
Gastrointestinal hormones	Notes
Gastrointestinal physiology: enzymes	Notes
GMC guidance: Confidentiality	Notes
Growth hormone	Notes
Hazard ratio	Notes
Hereditary angioedema	Notes
Hereditary haemorrhagic telangiectasia	Notes
HIV: immunology	Notes
HIV: the virus	Notes
HLA associations	Notes
Hypercalcaemia: management	Notes
Hyperkalaemia	Notes
Hyponatraemia	Notes
Hypersensitivity	Notes
Hyperuricaemia	Notes
Hypocalcaemia: causes and management	Notes
Hypocalcaemia: features	Notes
Hypokalaemia	Notes
Hyponatraemia	Notes
Hyponatraemia: correction	Notes
Hypophosphataemia	Notes
IL-1	Notes
Immune system cells: innate immune response	Notes
Immunoglobulins	Notes
Immunoglobulins: therapeutics	Notes
Incidence and prevalence	Notes
Inherited metabolic disorders	Notes
Intention to treat analysis	Notes
Iron metabolism	Notes
Kallman's syndrome	Notes
Klinefelter's syndrome	Notes
Latex allergy	Notes

Leukotrienes	Notes
Lower back pain	Notes
Lower back pain: prolapsed disc	Notes
Lung cancer: referral	Notes
Macroglossia	Notes
Marfan's syndrome	Notes
Membrane receptors	Notes
Menstrual cycle	Notes
Metabolic alkalosis	Notes
Methaemoglobinaemia	Notes
Mitochondrial diseases	Notes
Molecular biology techniques	Notes
Monoclonal antibodies	Notes
Neurofibromatosis	Notes
Nitric oxide	Notes
Noonan's syndrome	Notes
Normal distribution	Notes
Numbers needed to treat and absolute risk reduction	Notes
Obesity: physiology	Notes
Odds and odds ratio	Notes
Osteogenesis imperfecta	Notes
Osteomalacia	Notes
Oxygen dissociation curve	Notes
p53	Notes
PCR	Notes
Phenylketonuria	Notes
Porphyrias	Notes
Positron Emission Tomography (PET)	Notes
Prader-Willi syndrome	Notes
Pre- and post- test odds and probability	Notes
Pre-eclampsia	Notes
Prediabetes and impaired glucose regulation	Notes
Premature ovarian failure	Notes
Progestogen only pill: advantages/disadvantages	Notes
Prolactin and galactorrhoea	Notes
Pseudohypoparathyroidism	Notes
Pseudoxanthoma elasticum	Notes
Pulmonary capillary wedge pressure	Notes
Pulmonary surfactant	Notes
Radial nerve	Notes
Ramsay Hunt syndrome	Notes
Relative risk	Notes
Renal anatomy	Notes
Renal transplant: HLA typing and graft failure	Notes
Renin	Notes

Renin-angiotensin-aldosterone system	Notes
Respiratory physiology	Notes
Respiratory physiology: control	Notes
Respiratory physiology: hypoxia	Notes
Respiratory physiology: lung compliance	Notes
Respiratory physiology: lung volumes	Notes
Screening test statistics	Notes
Screening: Wilson and Junger criteria	Notes
Second messengers	Notes
SIADH: causes	Notes
Significance tests	Notes
Significance tests: types	Notes
Skewed distributions	Notes
SLE: features	Notes
Splenomegaly	Notes
Stevens-Johnson syndrome	Notes
Study design	Notes
Study design: evidence and recommendations	Notes
Study design: new drugs	Notes
T-Helper cells	Notes
Thiazide diuretics	Notes
Trimethoprim	Notes
Trinucleotide repeat disorders	Notes
Tumour suppressor genes	Notes
Turner's syndrome	Notes
Ulnar nerve	Notes
Upper limb anatomy	Notes
Valsalva manoeuvre	Notes
Vitamin C (ascorbic acid)	Notes
Vitamin D	Notes
Vitamin D-resistant rickets	Notes
Vitamin deficiency	Notes
Wiskott-Aldrich syndrome	Notes
X-linked dominant	Notes
X-linked recessive	Notes
X-linked recessive conditions	Notes

Achondroplasia

Achondroplasia is an autosomal dominant disorder associated with short stature. It is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR-3) gene. **This results in abnormal cartilage giving rise to:**

- short limbs (rhizomelia) with shortened fingers (brachydactyly)
- large head with frontal bossing
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis

Acute intermittent porphyria

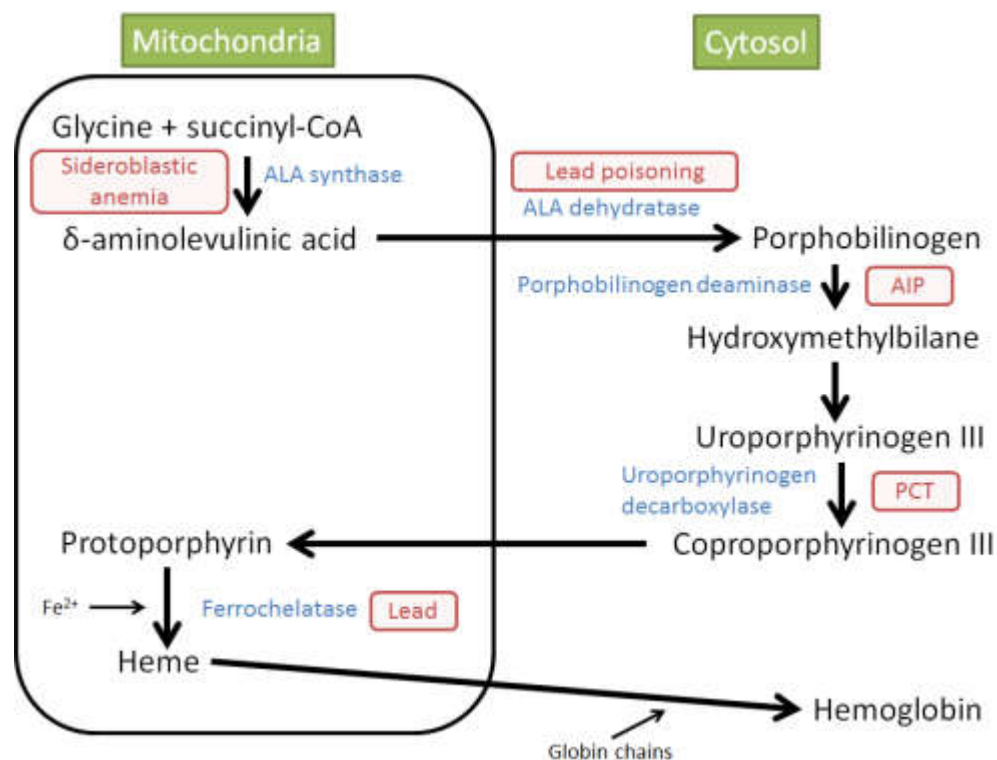
Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Features

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

Diagnosis

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen



External Links

[Royal College of Physicians](#)

2012 The acute porphyrias

Acute liver failure

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes

- paracetamol overdose
- alcohol
- viral hepatitis (usually A or B)
- acute fatty liver of pregnancy.

Chapter: clinical science

Features*

- jaundice
- coagulopathy: raised prothrombin time
- hypoalbuminaemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

*remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the prothrombin time and albumin level.

Acute phase proteins

Acute phase proteins

- CRP
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component*
- haptoglobin
- complement.

Chapter: clinical science

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). **Examples include:**

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

*plays a more significant role in other mammals such as mice

Adrenal medulla

The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline. It essentially represents an enlarged and specialised sympathetic ganglion

Adrenoceptor agonists

Alpha-1 agonists

- phenylephrine

Alpha-2 agonists

- clonidine

Beta-1 agonists

- dobutamine

Chapter: clinical science

Beta-2 agonists

- salbutamol

Beta-3 agonists

- being developed, may have a role in preventing obesity (stimulation causes lipolysis)
-

Adrenoceptor antagonists

Alpha antagonists

- alpha-1: doxazosin
- alpha-1a: tamsulosin - acts mainly on urogenital tract
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

Adrenoceptors

Alpha-1

- vasoconstriction
- relaxation of GI smooth muscle
- salivary secretion
- hepatic glycogenolysis

Alpha-2

- mainly presynaptic: inhibition of transmitter release (inc NA, Ach from autonomic nerves)
- inhibits insulin
- platelet aggregation

Beta-1

- mainly located in the heart
- increase heart rate + force

Beta-2

- vasodilation
- bronchodilation
- relaxation of GI smooth muscle

Beta-3

- lipolysis

Pathways

- all are G-protein coupled
- alpha-1: activate phospholipase C → IP3 → DAG
- alpha-2: inhibit adenylate cyclase
- beta-1: stimulate adenylate cyclase
- beta-2: stimulate adenylate cyclase
- beta-3: stimulate adenylate cyclase

Altitude related disorders

There are three main types of altitude related disorders: acute mountain sickness (AMS), which may progress to high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness is generally a self-limiting condition. Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:

- headache
- nausea
- fatigue

Prevention and treatment of AMS

- the risk of AMS may actually be positively correlated to physical fitness
- gain altitude at no more than 500 m per day
- acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
- treatment: descent.

Chapter: clinical science

♦A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE), potentially fatal conditions

- HAPE presents with classical pulmonary oedema features
- HACE presents with headache, ataxia, papilloedema

Management of HACE

- descent
- dexamethasone

Management of HAPE

- descent
- nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors*
- oxygen if available

*the relative merits of these different treatments has only been studied in small trials. All seem to work by reducing systolic pulmonary artery pressure

Anaphylaxis

♦Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

♦Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication. The Resuscitation Council guidelines on anaphylaxis have recently been updated. Adrenaline is by far the most important drug in anaphylaxis and should be given as soon as possible. **The recommended doses for adrenaline, hydrocortisone and chlorphenamine are as follows:**

	Adrenaline	Hydrocortisone	Chlorphenamine
< 6 months	150 micrograms (0.15ml 1 in 1,000)	25 mg	250 micrograms/kg
6 months - 6 years	150 micrograms (0.15ml 1 in 1,000)	50 mg	2.5 mg
6-12 years	300 micrograms (0.3ml 1 in 1,000)	100 mg	5 mg
Adult and child > 12 years	500 micrograms (0.5ml 1 in 1,000)	200 mg	10 mg

Adrenaline can be repeated every 5 minutes if necessary. The best site for IM injection is the anterolateral aspect of the middle third of the thigh.

Common identified causes of anaphylaxis:

- food (e.g. Nuts) - the most common cause in children
- drugs
- venom (e.g. Wasp sting)

♦Sometimes it can be difficult to establish whether a patient had a true episode of anaphylaxis. Serum tryptase levels are sometimes taken in such patients as they remain elevated for up to 12 hours following an acute episode of anaphylaxis.

External Links

[Resus Council](#)

Anaphylaxis guidelines

ANCA

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) - cytoplasmic (cANCA) and perinuclear (pANCA)

For the exam, remember:

- cANCA - Wegener's granulomatosis
- pANCA - Churg-Strauss syndrome + others (see below)

cANCA

- most common target serine proteinase 3 (PR3)
- some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
- microscopic polyangiitis, positive in 40%

pANCA

- most common target is myeloperoxidase (MPO)
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%.

Other causes of positive ANCA (usually pANCA):

- inflammatory bowel disease (UC > Crohn's)
 - connective tissue disorders: RA, SLE, Sjogren's
 - autoimmune hepatitis
-

Angiodysplasia

Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia. There is thought to be an association with aortic stenosis, although this is debated. Angiodysplasia is generally seen in elderly patients

Diagnosis

- colonoscopy
- mesenteric angiography if acutely bleeding

Management

- endoscopic cautery or argon plasma coagulation
 - antifibrinolytics e.g. Tranexamic acid
 - oestrogens may also be used
-

Anion gap

The anion gap is calculated by:

(sodium + potassium) - (bicarbonate + chloride)

A normal anion gap is 8-14 mmol/L

It is useful to consider in patients with a metabolic acidosis:

Causes of a normal anion gap or hyperchloraemic metabolic acidosis:

- gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease

Causes of a raised anion gap metabolic acidosis

- lactate: shock, hypoxia
 - ketones: diabetic ketoacidosis, alcohol
 - urate: renal failure
 - acid poisoning: salicylates, methanol
-

Antidiuretic hormone

Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.

	Notes	Further detail
Source	Synthesized in the supraoptic nuclei of the hypothalamus, released by the pituitary pituitary	
Function	Conserves body water	Promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels
Regulation	Increases secretion • extracellular fluid osmolality increase • volume decrease • pressure decrease • angiotensin II Decreases secretion • extracellular fluid osmolality decrease • volume increase • temperature decrease	Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI) Cranial DI can be treated by desmopressin, an analog of ADH

Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
Aciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	HSV, VZV	Crystalline nephropathy
Ganciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	CMV	Myelosuppression/agranulocytosis
Ribavirin	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA	Chronic hepatitis C, RSV	Haemolytic anaemia
Amantadine	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
Oseltamivir	Inhibits neuraminidase	Influenza	
Foscarnet	Pyrophosphate analog which inhibits viral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures
Interferon-α	Human glycoproteins which inhibit synthesis of mRNA	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppression
Cidofovir	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity

Chapter: clinical science

Anti-retroviral agent used in HIV

Nucleoside analogue reverse transcriptase inhibitors (NRTI):

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
-

Arterial blood gas interpretation

The Resuscitation Council (UK) advocate a 5 step approach to arterial blood gas interpretation.

1. How is the patient?

2. Is the patient hypoxaemic?

- the PaO_2 on air should be >10 kPa

3. Is the patient acidaemic ($\text{pH} < 7.35$) or alkalaemic ($\text{pH} > 7.45$)

4. Respiratory component: What has happened to the PaCO_2 ?

- $\text{PaCO}_2 > 6.0$ kPa suggests a respiratory acidosis (or respiratory compensation for a metabolic alkalosis)
- $\text{PaCO}_2 < 4.7$ kPa suggests a respiratory alkalosis (or respiratory compensation for a metabolic acidosis)

5. Metabolic component: What is the bicarbonate level/base excess?

- bicarbonate < 22 mmol/l (or a base excess < -2 mmol/l) suggests a metabolic acidosis (or renal compensation for a respiratory alkalosis)
- bicarbonate > 26 mmol/l (or a base excess $> +2$ mmol/l) suggests a metabolic alkalosis (or renal compensation for a respiratory acidosis)

ROME

Respiratory = Opposite

- low pH + high PaCO_2 i.e. acidosis, or
- high pH + low PaCO_2 i.e. alkalosis

Metabolic = Equal

- low pH + low bicarbonate i.e. acidosis, or
- high pH + high bicarbonate i.e. alkalosis

Atherosclerosis

Atherosclerosis is a complex process which develops over a number of years. A number of changes can be seen:

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

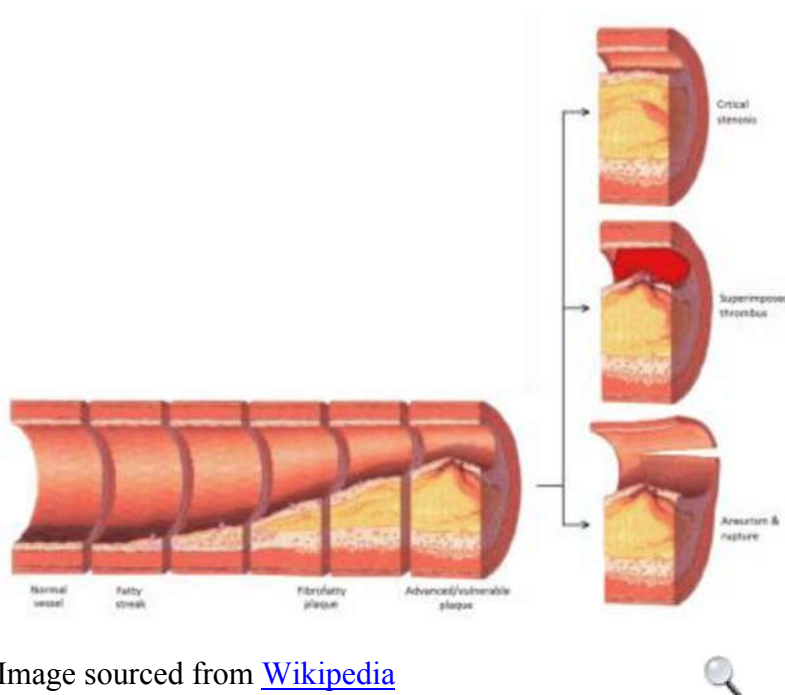


Image sourced from [Wikipedia](#)

Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.

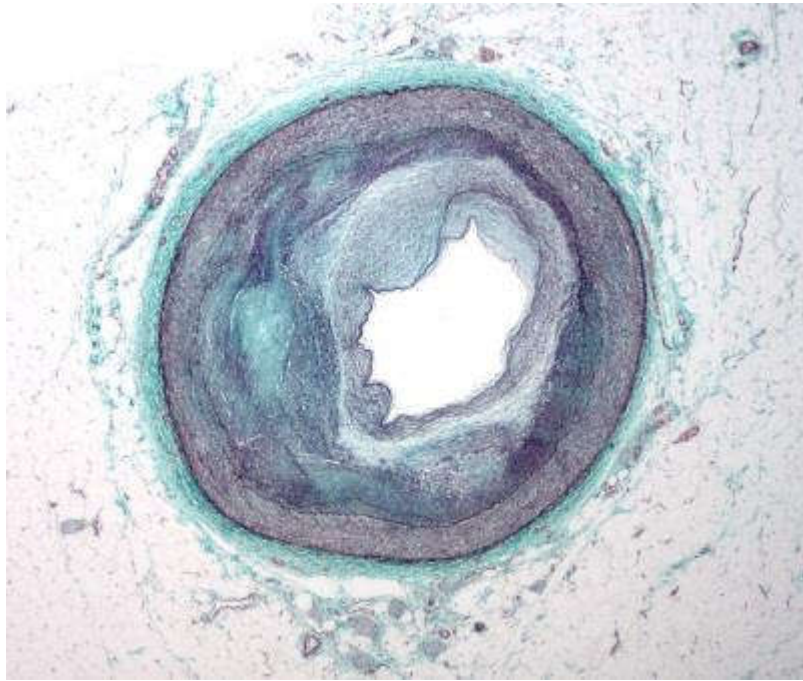


Image sourced from [Wikipedia](#)

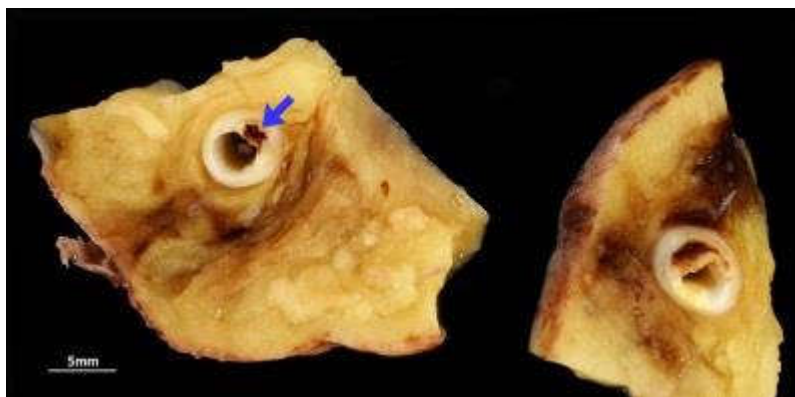


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

Complications of atherosclerosis

Taking the coronary arteries as an example, once a plaque has formed a number of complications can develop:

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction



© Image used on license from PathoPic



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.



© Image used on license from PathoPic



Pathological specimen showing infarction of the anteroapical and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

Atrial natriuretic peptide

Basics

- secreted mainly from myocytes of right atrium and ventricle in response to increased blood volume
- secreted by both the right and left atria (right >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- degraded by endopeptidases

Actions

- natriuretic, i.e. promotes excretion of sodium
 - lowers BP
 - antagonises actions of angiotensin II, aldosterone
-

Atropine

Atropine is an antagonist of the muscarinic acetylcholine receptor

Uses*

- treatment of organophosphate poisoning

Physiological effects

- tachycardia
- mydriasis

*atropine is no longer used in resuscitation

Autosomal dominant

In autosomal dominant diseases:

- both homozygotes and heterozygotes manifest disease (there is no carrier state)
- both males and females affected
- only affected individuals can pass on disease
- disease is passed on to 50% of children
- normally appears in every generation (although see below)
- risk remains same for each successive pregnancy

Complicating factors:

- non-penetrance: lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

Autosomal dominant conditions

Autosomal **recessive** conditions are often thought to be '**metabolic**' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

Chapter: clinical science

The following conditions are autosomal dominant:

- Achondroplasia
- Acute intermittent porphyria
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis
- Hereditary haemorrhagic telangiectasia
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- Hyperlipidaemia type II
- Hypokalaemic periodic paralysis
- Malignant hyperthermia
- Marfan's syndromes
- Myotonic dystrophy
- Neurofibromatosis
- Noonan syndrome
- Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- Tuberose sclerosis
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

Autosomal recessive

In autosomal recessive inheritance:

- only homozygotes are affected
- males and females are equally likely to be affected
- not manifest in every generation - may 'skip a generation'

If two heterozygote parents

- 25% chance of having an affected (homozygote) child
- 50% chance of having a carrier (heterozygote) child
- 25% chance of having an unaffected (i.e. genotypical) child

If one affected parent (i.e. homozygote for gene) and one unaffected (i.e. not a carrier or affected)

- all the children will be carriers

Autosomal recessive disorders are often metabolic in nature and are generally more life-threatening compared to autosomal dominant conditions

Autosomal recessive conditions

Autosomal **recessive** conditions are often thought to be '**metabolic**' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are autosomal recessive:

- Albinism
- Ataxia telangiectasia
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- Friedreich's ataxia
- Gilbert's syndrome*
- Glycogen storage disease
- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- Sickle cell anaemia
- Thalassaemias
- Wilson's disease

*this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant

Avascular necrosis

Avascular necrosis (AVN) may be defined as death of bone tissue secondary to loss of the blood supply. This leads to bone destruction and loss of joint function. It most commonly affects the epiphysis of long bones such as the femur.

Causes

- long-term steroid use
- chemotherapy
- alcohol excess
- trauma

Features

- initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially
 - MRI is the investigation of choice. It is more sensitive than radionuclide bone scanning
-

B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain.

Whilst heart failure is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as myocardial ischaemia or valvular disease may raise levels. Raised levels may also be seen due to reduced excretion in patients with chronic kidney disease. Factors which reduce BNP levels include treatment with ACE inhibitors, angiotensin-2 receptor blockers and diuretics.

Effects of BNP

- vasodilator
- diuretic and natriuretic
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

Clinical uses of BNP

Diagnosing patients with acute dyspnoea

- a low concentration of BNP(< 100pg/ml) makes a diagnosis of heart failure unlikely, but raised levels should prompt further investigation to confirm the diagnosis
- NICE currently recommends BNP as a helpful test to rule out a diagnosis of heart failure

Prognosis in patients with chronic heart failure

- initial evidence suggests BNP is an extremely useful marker of prognosis

Guiding treatment in patients with chronic heart failure

- effective treatment lowers BNP levels.

Screening for cardiac dysfunction

- not currently recommended for population screening.

Calcium metabolism

The two hormones which primarily control calcium metabolism are:

- parathyroid hormone (PTH)
- 1,25-dihydroxycholecalciferol (calcitriol, the active form of vitamin D)

Other hormones include

- calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
- thyroxine
- growth hormone

Actions of parathyroid hormone

- increases plasma calcium, decreases plasma phosphate
- increases renal tubular reabsorption of calcium
- increases osteoclastic activity*
- increases renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
- decreases renal phosphate reabsorption

Actions of 1,25-dihydroxycholecalciferol

- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

*this is actually via an indirect mechanism as osteoclasts don't have PTH receptors

Cardiac action potential

Cardiac action potential

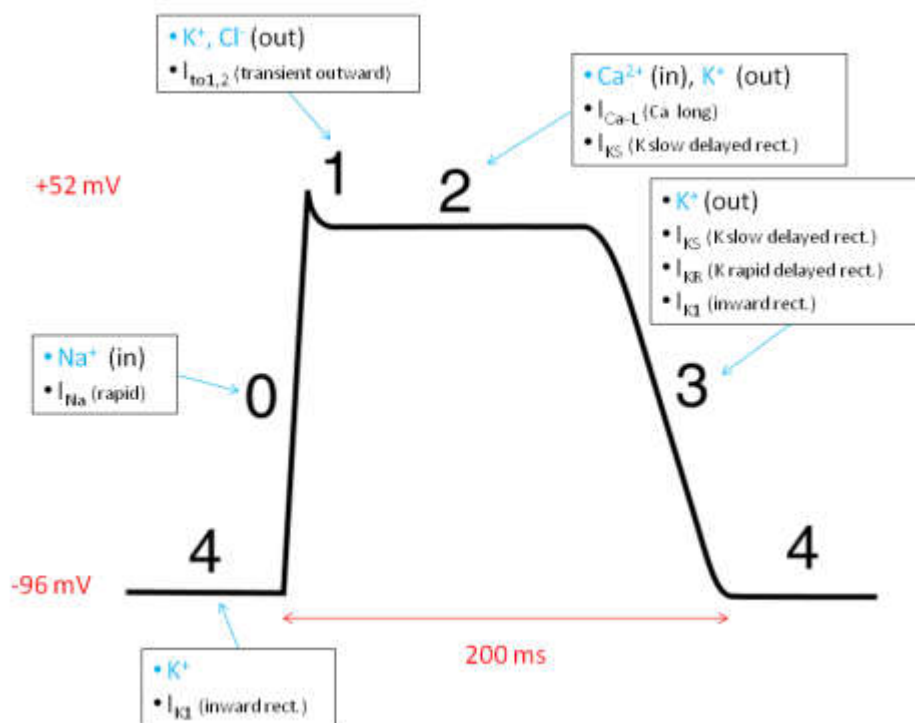


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/Cardiac_action_potential)

Phase	Description	Mechanism
0	Rapid depolarisation	Rapid sodium influx These channels automatically deactivate after a few ms
1	Early repolarisation	Efflux of potassium
2	Plateau	Slow influx of calcium
3	Final repolarisation	Efflux of potassium
4	Restoration of ionic concentrations	Resting potential is restored by Na^+/K^+ ATPase There is slow entry of Na^+ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle.

Conduction velocity

Site	Speed
Atrial conduction	Spreads along ordinary atrial myocardial fibres at 1 m/sec
AV node conduction	0.05 m/sec
Ventricular conduction	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this allows a rapid and coordinated contraction of the ventricles)

Cardiac imaging: non-invasive techniques excluding echocardiography

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

Nuclear imaging

These techniques use radiotracers which are extracted by normal myocardium. **Examples include:**

- thallium
- technetium (99mTc) sestamibi: a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
- fluorodeoxyglucose (FDG): used in Positron Emission Tomography (PET) scans

The primary role of SPECT is to assess myocardial perfusion and myocardial viability. Two sets of images are usually acquired. First the myocardium at rest followed by images of the myocardium during stress (either exercise or following adenosine / dipyridamole). By comparing the rest with stress images any areas of ischaemia can be classified as reversible or fixed (e.g. Following a myocardial infarction). Cardiac PET is predominately a research tool at the current time

MUGA

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- radionuclide (technetium-99m) is injected intravenously
- the patient is placed under a gamma camera
- may be performed as a stress test
- can accurately measure left ventricular ejection fraction. Typically used before and after cardiotoxic drugs are used.

Cardiac Computed Tomography (CT)

Cardiac CT is useful for assessing suspected ischaemic heart disease, **using two main methods:**

- calcium score: there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events. Cardiac CT can quantify the amount of calcium producing a 'calcium score'
- contrast enhanced CT: allows visualisation of the coronary artery lumen

If these two techniques are combined cardiac CT has a very high negative predictive value for ischaemic heart disease.

Cardiac MRI

Cardiac MRI (commonly termed CMR) has become the gold standard for providing structural images of the heart. It is particularly useful when assessing congenital heart disease, determining right and left ventricular mass and differentiating forms of cardiomyopathy. Myocardial perfusion can also be assessed following the administration of gadolinium. Currently CMR provides limited data on the extent of coronary artery disease.

Please also see the British Heart Foundation link for an excellent summary.

External Links

[Royal College of Physicians](#)

2012 Nuclear cardiology review

Cardiovascular physiology

Left ventricular ejection fraction

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume) * 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

Pulse pressure

Pulse pressure = Systolic Pressure - Diastolic Pressure

Factors which increase pulse pressure:

- a less compliant aorta (this tends to occur with advancing age)
- increased stroke volume

Cell cycle

The cell cycle is regulated by proteins called cyclins which in turn control cyclin-dependent kinase (CDK) enzymes.

Phase	Notes	Regulatory proteins
G ₀	'resting' phase - quiescent cells such as hepatocytes and more permanently resting cells such as neurons	
G ₁	- Gap 1, cells increase in size - determines length of cell cycle - under influence of p53	Cyclin D / CDK4, Cyclin D / CDK6 and Cyclin E / CDK2: regulates transition from G ₁ to S phase
S	- Synthesis of DNA, RNA and histone - centrosome duplication	Cyclin A / CDK2: active in S phase
G ₂	Gap 2, cells continue to increase in size	Cyclin B / CDK1: regulates transition from G ₂ to M phase
M	- Mitosis - cell division - the shortest phase of the cell cycle	

Cell division

There are two types of cell division; mitosis and meiosis.

The table below demonstrates the key differences:

Mitosis	Meiosis
Occurs in somatic cells	Occurs in gametes
Results in 2 diploid daughter cells	Results in 4 haploid daughter cells
Daughter cells are genetically identical to parent cell	Daughter cells contain one homologue of each chromosome pair and are therefore genetically different

Remember:

- somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX
- cells with a normal chromosome complement are known as diploid cells
- gametes (ova or spermatozoa) have a single copy of each chromosome and are known as haploid cells

Mitosis

Mitosis occurs during the M phase of the cell cycle. It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells. This allows tissue to grow and renew itself.

During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes. **The table below shows the phases of mitosis itself:**

Prophase	Chromatin in the nucleus condenses
Prometaphase	Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes
Metaphase	Chromosomes aligned at middle of cell
Anaphase	The paired chromosomes separate at the kinetochores and move to opposite sides of the cell
Telophase	Chromatids arrive at opposite poles of cell
Cytokinesis	Actin-myosin complex in the centre of the cell contracts resulting in it being 'pinched' into two daughter cells

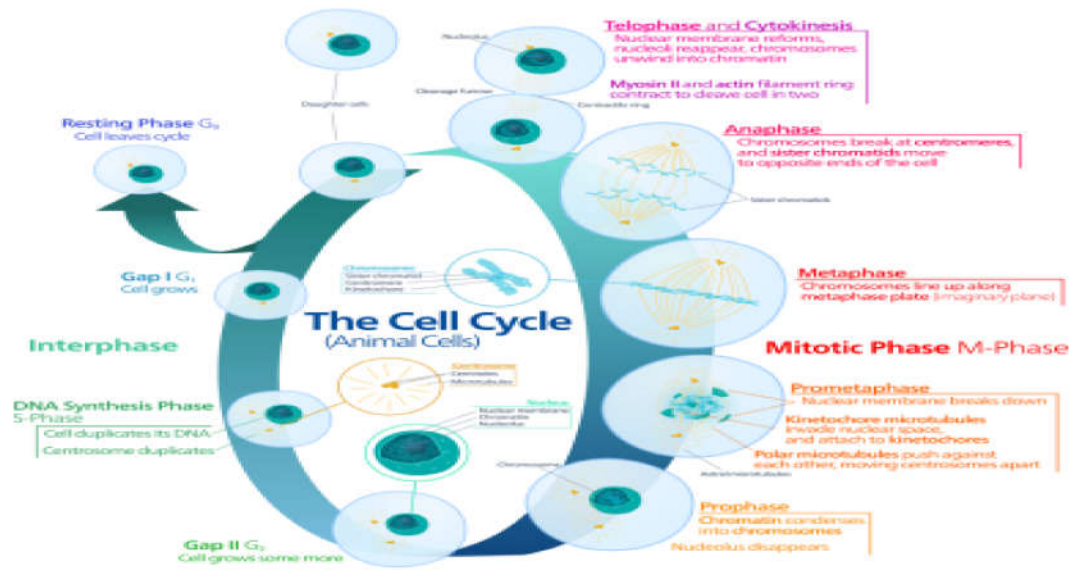


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/File:Cellcycle.svg)

Cell organelles

The table below summarises the main functions of the major cell organelles:

Organelle/macromolecule	Main function
Endoplasmic reticulum	Rough endoplasmic reticulum - translation and folding of new proteins - manufacture of lysosomal enzymes - site of N-linked glycosylation - examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells Smooth endoplasmic reticulum - steroid, lipid synthesis - examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries

Chapter: clinical science

Golgi apparatus	Modifies, sorts, and packages these molecules that are destined for cell secretion Site of O-linked glycosylation
Mitochondrion	Aerobic respiration. Contains mitochondrial genome as circular DNA
Nucleus	DNA maintenance and RNA transcription
Lysosome	Breakdown of large molecules such as proteins and polysaccharides
Nucleolus	Ribosome production
Ribosome	Translation of RNA into proteins
Peroxisome	Catabolism of very long chain fatty acids and amino acids Results in the formation of hydrogen peroxide
Proteasome	Along with the lysosome pathway involved in degradation of protein molecules that have been tagged with ubiquitin

Cell surface proteins

The table below shows the most common cell surface proteins associated with particular cell types:

Type of cell	Cell surface markers
Haematopoietic stem cells	CD34
Helper T cell	CD4, TCR, CD3, CD28
Cytotoxic T cell	CD8, TCR, CD3, CD28
Regulatory T cell	CD4, CD25, TCR, CD3, CD28
B cell	CD19, CD20, CD40, MHC II, B7
Macrophage	CD14, CD40, MHC II, B7
Natural killer cell	CD16, CD56

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells
CD5	Found in the majority of mantle cell lymphomas
CD8	Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells
CD14	Cell surface marker for macrophages
CD15	Expressed on Reed-Sternberg cells (along with CD30)
CD16	Bind to the Fc portion of IgG antibodies
CD21	Receptor for Epstein-Barr virus
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD45	Protein tyrosine phosphatase present on all leucocytes
CD56	Unique marker for natural killer cells
CD95	Acts as the FAS receptor, involved in apoptosis

Cervical cancer

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. **It may be divided into:**

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papilloma virus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

External Links

[NICE Clinical Knowledge Summaries](#)

Cervical cancer management guidelines

[Cancer Research UK](#)

Cervical cancer

Chronic kidney disease: bone disease

Basic problems in chronic kidney disease

- low vitamin D (1-alpha hydroxylation normally occurs in the kidneys)
- high phosphate
- low calcium: due to lack of vitamin D, high phosphate
- secondary hyperparathyroidism: due to low calcium, high phosphate and low vitamin D

Several clinical manifestations may result:

Osteitis fibrosa cystica

- aka hyperparathyroid bone disease

Adynamic

- reduction in cellular activity (both osteoblasts and osteoclasts) in bone
- may be due to over treatment with vitamin D

Osteomalacia

- due to low vitamin D

Osteosclerosis

Osteoporosis



© Image used on license from [Radiopaedia](#)



X-ray of a Brown tumour caused by secondary hyperparathyroidism in a young female with chronic kidney disease

External Links

[Royal College of Physicians](#)

2012 Hyperparathyroidism in chronic kidney disease

Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into • IIa - assesses optimal dosing • IIb - assesses efficacy
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side-effects

Cocaine

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
- both tachycardia and bradycardia may occur
- hypertension
- QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia

Psychiatric effects

- agitation
- psychosis
- hallucinations

Others

- ischaemic colitis is recognised in patients following cocaine ingestion. This should be considered if patients complain of abdominal pain or rectal bleeding
- hyperthermia
- metabolic acidosis
- rhabdomyolysis

Management of cocaine toxicity

- in general benzodiazepines are generally first-line for most cocaine related problems
- chest pain: benzodiazepines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazepines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

Colorectal cancer: referral guidelines

NICE updated their referral guidelines in 2015. **The following patients should be referred urgently (i.e. within 2 weeks) to colorectal services for investigation:**

- patients ≥ 40 years with unexplained weight loss **AND** abdominal pain
- patients ≥ 50 years with unexplained rectal bleeding
- patients ≥ 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

An urgent referral (within 2 weeks) should be 'considered' if:

- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding **AND** any of the following unexplained symptoms/findings:
 - --> abdominal pain
 - --> change in bowel habit
 - --> weight loss
 - --> iron deficiency anaemia

Faecal Occult Blood Testing (FOBT)

This was one of the main changes in 2015. Remember that the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening.

In addition FOBT should be offered to:

- patients $\geq$ 50 years with unexplained abdominal pain **OR** weight loss
- patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
- patients $\geq$ 60 years who have anaemia even in the absence of iron deficiency

External Links

[NICE](#)

Cancer referral guidelines

Common peroneal nerve lesion

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

The most characteristic feature of a common peroneal nerve lesion is foot drop

Other features include:

- weakness of foot dorsiflexion
- weakness of foot eversion
- weakness of extensor hallucis longus
- sensory loss over the dorsum of the foot and the lower lateral part of the leg
- wasting of the anterior tibial and peroneal muscles

Complement deficiencies

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. Complement proteins are involved in chemotaxis, cell lysis and opsonisation

C1 inhibitor (C1-INH) protein deficiency

- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura

C3 deficiency

- causes recurrent bacterial infections

C5 deficiency

- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
 - particularly prone to *Neisseria meningitidis* infection
-

Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia. It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury. CRPS is 3 times more common in women.

There are two types of CRPS:

- type I (most common): there is no demonstrable lesion to a major nerve
- type II: there is a lesion to a major nerve

Features

- progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- temperature and skin colour changes
- oedema and sweating
- motor dysfunction
- the Budapest Diagnostic Criteria are commonly used in the UK

Management

- early physiotherapy is important
 - neuropathic analgesia in-line with NICE guidelines
 - specialist management (e.g. Pain team) is required
-

External Links

[Royal College of Physicians](#)

RCP Guidelines on CRPS

Confidence interval and standard error of the mean

The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- a formal definition may be: *a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits**
- in simpler terms: a range of values within which the true effect of intervention is likely to lie

The likelihood of the true effect lying within the confidence interval is determined by the confidence level. For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

How is the confidence interval calculated?

The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean

Key point

- $SEM = SD / \text{square root } (n)$
- where SD = standard deviation and n = sample size
- therefore the SEM gets smaller as the sample size (n) increases

A 95% confidence interval:

- lower limit = mean - (1.96 * SEM)
- upper limit = mean + (1.96 * SEM)

Chapter: clinical science

The above formula is a slight simplification:

- if a small sample size is used (e.g. $n < 100$) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value
- if a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would be 1.645

Results such as mean value are often presented along with a confidence interval. For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (± 2 SE).

*Last JM. A dictionary of epidemiology. Oxford: International Journal of Epidemiology, 1988

COPD: causes

Smoking!

Alpha-1 antitrypsin deficiency

Other causes

- cadmium (used in smelting)
 - coal
 - cotton
 - cement
 - grain
-

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder causing increased viscosity of secretions (e.g. lungs and pancreas). It is due to a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR), which codes a cAMP-regulated chloride channel

In the UK 80% of CF cases are due to delta F508 on the long arm of chromosome 7. Cystic fibrosis affects 1 per 2500 births, and the carrier rate is c. 1 in 25

Organisms which may colonise CF patients:

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Burkholderia cepacia**
- *Aspergillus*

*previously known as *Pseudomonas cepacia*

Cystinuria

Cystinuria is an autosomal recessive disorder characterised by the formation of recurrent renal stones. It is due to a defect in the membrane transport of cystine, ornithine, lysine, arginine (mnemonic = COLA)

Genetics

- chromosome 2: SLC3A1 gene, chromosome 19: SLC7A9

Features

- recurrent renal stones
- are classically yellow and crystalline, appearing semi-opaque on x-ray.

Diagnosis

- cyanide-nitroprusside test

Management

- hydration
 - D-penicillamine
 - urinary alkalization
-

DiGeorge syndrome

DiGeorge syndrome is a primary immunodeficiency disorder caused by T-cell deficiency and dysfunction. It is an example of a microdeletion syndrome

Features

- at risk of viral and fungal infections
 - parathyroid gland hypoplasia → hypocalcaemic tetany
 - thymus hypoplasia
 - T-lymphocyte deficiency/dysfunction
-

Down's syndrome: epidemiology and genetics

Risk of Down's syndrome with increasing maternal age

Age (years)	Risk
20	1 in 1,500
30	1 in 800
35	1 in 270
40	1 in 100
45	1 in 50 or greater

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-disjunction	94%	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher

Endothelin

Endothelin is a potent, long-acting vasoconstrictor and bronchoconstrictor. It is secreted initially as a prohormone by the vascular endothelium and later converted to ET-1 by the action of endothelin converting enzyme. It acts via interaction with a G-protein linked to phospholipase C leading to calcium release. Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's.

Chapter: clinical science

Promotes release

- angiotensin II
- ADH
- hypoxia
- mechanical shearing forces

Inhibits release

- nitric oxide
- prostacyclin

Raised levels in

- MI
 - heart failure
 - ARF
 - asthma
 - primary pulmonary hypertension
-

Energy from food

The amount of energy that may be derived from 1 gram of food is as follows:

- carbohydrates: 4 kcal
 - protein: 4 kcal
 - fat: 9 kcal
-

Epidermis

The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina

It may be divided in to five layers:

Layer	Description
Stratum corneum	Flat, dead, scale-like cells filled with keratin Continually shed
Stratum lucidum	Clear layer - present in thick skin only
Stratum granulosum	Cells form links with neighbours
Stratum spinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis
Stratum germinativum	The basement membrane - single layer of columnar epithelial cells Gives rise to keratinocytes Contains melanocytes

Erythrocyte sedimentation rate (ESR)

The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of red blood cells and the concentration of plasma proteins such as fibrinogen, alpha2-globulins and gamma globulins

Causes of a high ESR

- temporal arteritis
- myeloma
- other connective tissue disorders e.g. systemic lupus erythematosus
- other malignancies
- infection
- other factors which raise ESR: increasing age, female sex, anaemia

Causes of a low ESR

- polycythaemia
- afibrinogenaemia/hypofibrinogenaemia

Folate metabolism

Drugs which interfere with metabolism

- trimethoprim
- methotrexate
- pyrimethamine

Drugs which can reduce absorption

- phenytoin

Food energy

The amount of energy a food product contains is expressed in calories (kcal).

In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

Foramina of the skull

Questions asking about foramina of the skull have come up in the exam in previous years. Below is a brief summary of the major foramina, please see the Wikipedia link for a full list.

Foramen	Bone	Vessels	Nerves
Optic canal	Sphenoid	Ophthalmic artery	Optic nerve (II)
Superior orbital fissure	Sphenoid	Superior ophthalmic vein Inferior ophthalmic vein	Oculomotor nerve (III) Trochlear nerve (IV) lacrimal, frontal and nasociliary branches of ophthalmic nerve (V1) Abducent nerve (VI)
Inferior orbital fissure	Sphenoid and maxilla	Inferior ophthalmic veins Infraorbital artery Infraorbital vein	Zygomatic nerve and infraorbital nerve of maxillary nerve (V2) Orbital branches of pterygopalatine ganglion
Foramen rotundum	Sphenoid	-	Maxillary nerve (V2)
Foramen ovale	Sphenoid	Accessory meningeal artery	Mandibular nerve (V3)
Jugular foramen	Occipital and temporal	Posterior meningeal artery Ascending pharyngeal artery Inferior petrosal sinus Sigmoid sinus Internal jugular vein	Glossopharyngeal nerve (IX) Vagus nerve (X) Accessory nerve (XI)

External Links

[Wikipedia](#)

Foramina of the skull

Fourth nerve palsy

Overview

- supplies superior oblique (depresses eye, moves inward)

Features

- vertical diplopia
- classically noticed when reading book or going down stairs

Fragile X

Fragile X is a trinucleotide repeat disorder

Features in males

- learning difficulties
- large low set ears, long thin face, high arched palate
- macroorchidism
- hypotonia
- autism is more common
- mitral valve prolapse

Features in females (who have one fragile chromosome and one normal X chromosome) range from normal to mild.

Diagnosis

- can be made antenatally by chorionic villus sampling or amniocentesis
- analysis of the number of CGG repeats using restriction endonuclease digestion and Southern blot analysis

Funnel plot

A funnel plot is primarily used to demonstrate the existence of publication bias in meta-analyses. Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation

- a symmetrical, inverted funnel shape indicates that publication bias is unlikely
- conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects')

External Links:

[Cochrane handbook](#)

Hypothetical funnel plots

[BMJ](#)

Funnel plots

Galactosaemia

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features

- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

Diagnosis

- urine reducing substances
Management is with a galactose free diet

Gastrointestinal hormones

Below is a brief summary of the major hormones involved in food digestion:

	Source	Stimulus	Actions
Gastrin	G cells in antrum of the stomach	Distension of stomach, vagus nerves (mediated by gastrin-releasing peptide), luminal peptides/amino acids Inhibited by: low antral pH, somatostatin	Increase HCL, pepsinogen and IF secretion, increases gastric motility, stimulates parietal cell maturation
CCK	I cells in upper small intestine	Partially digested proteins and triglycerides	Increases secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety
Secretin	S cells in upper small intestine	Acidic chyme, fatty acids	Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, decreases gastric acid secretion, trophic effect on pancreatic acinar cells
VIP	Small intestine, pancreas	Neural	Stimulates secretion by pancreas and intestines, inhibits acid secretion
Somatostatin	D cells in the pancreas & stomach	Fat, bile salts and glucose in the intestinal lumen	Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion inhibits trophic effects of gastrin, stimulates gastric mucous production

Gastrointestinal physiology: enzymes

Amylase is present in saliva and pancreatic secretions. It breaks starch down into sugar

The following brush border enzymes are involved in the breakdown of carbohydrates:

- maltase: cleaves disaccharide maltose to glucose + glucose
- sucrase: cleaves sucrose to fructose and glucose
- lactase: cleaves disaccharide lactose to glucose + galactose

GMC guidance: Confidentiality

We will not try to replicate the extensive guidance given by the General Medical Council here. There is a link available for more detailed information.

External Links

[GMC](#)

Confidentiality guidance

Growth hormone

Growth hormone (GH) is an anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It has actions on multiple organ systems and is important in postnatal growth and development. Growth hormone is also responsible for changes in protein, lipid, and carbohydrate metabolism

	Notes	Further detail
Source	Anterior pituitary	
Function	Postnatal growth and development Numerous actions on protein, carbohydrate and fat metabolism (including increasing lipolysis and gluconeogenesis)	Mechanism of action • acts on a transmembrane receptor for growth factor • binding of GH to the receptor leads to receptor dimerization • acts directly on tissues and also indirectly via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver

Chapter: clinical science

Regulation	<u>Increases secretion</u> • growth hormone releasing hormone (GHRH): released in pulses by the hypothalamus • fasting • exercise • sleep	Conditions associated with GH disorders □ excess GH: acromegaly □ GH deficiency: resulting in short stature
	<u>Decreases secretion</u> • glucose • somatostatin (itself increased by somatomedins, circulating insulin-like growth factors, IGF-1 and IGF-2)	

Hazard ratio

The hazard ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time.

Hereditary angioedema

Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of tissues.

Investigation

- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool.

Symptoms

- attacks may be preceded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

Management

- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

External Links:

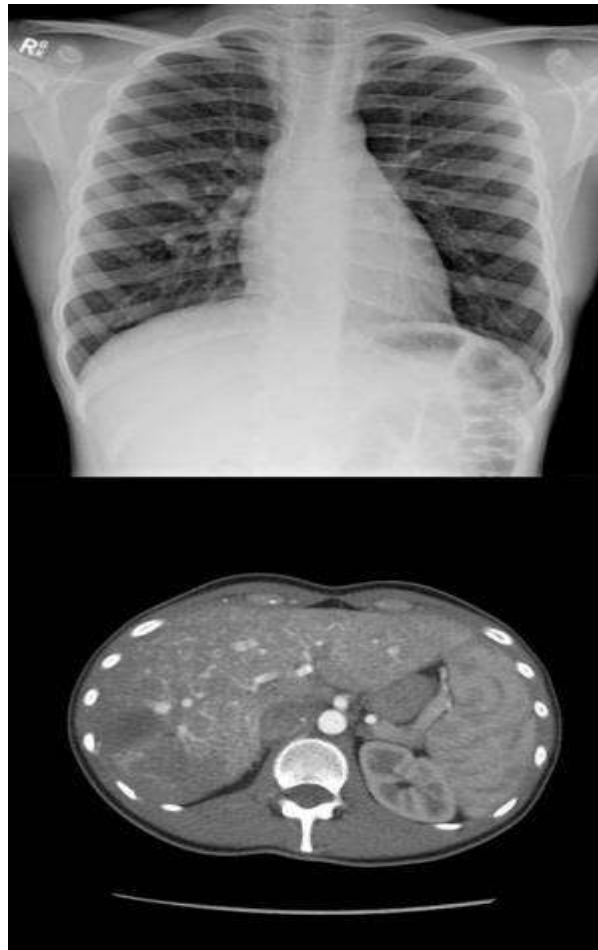
patient.co.uk

Hereditary hemorrhagic telangiectasia

Also known as **Osler-Weber-Rendu syndrome**, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- **epistaxis** : spontaneous, recurrent nosebleeds
- **telangiectases**: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- **visceral lesions**: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- **family history**: a first-degree relative with HHT



© Image used on license from [Radiopaedia](#) 

The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

External Links:

[DermNet NZ](#)

Hereditary haemorrhagic telangiectasia

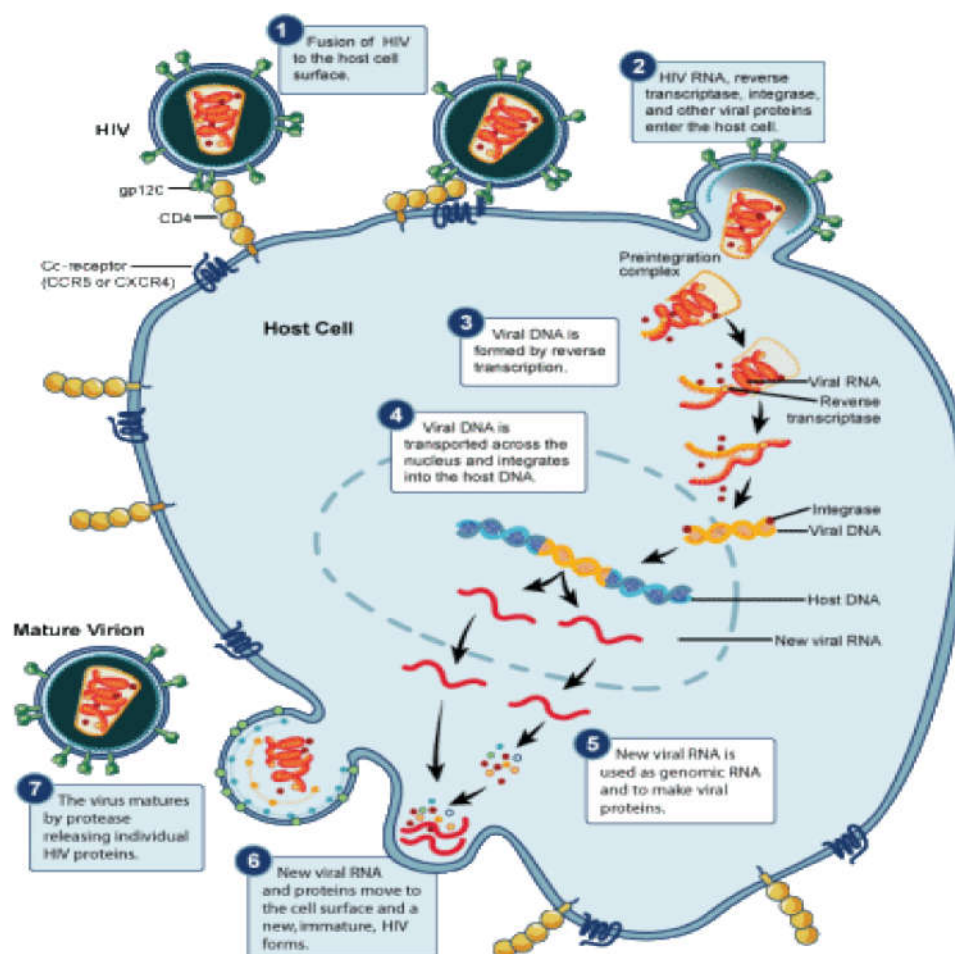
[Postgraduate Medical Journal](#)

Review of HHT

HIV: immunology

The following immunological changes are seen in progressive HIV:

- reduction in CD4 count
- increase B2-microglobulin
- decreased IL-2 production
- polyclonal B-cell activation
- decrease NK cell function
- reduced delayed hypersensitivity responses

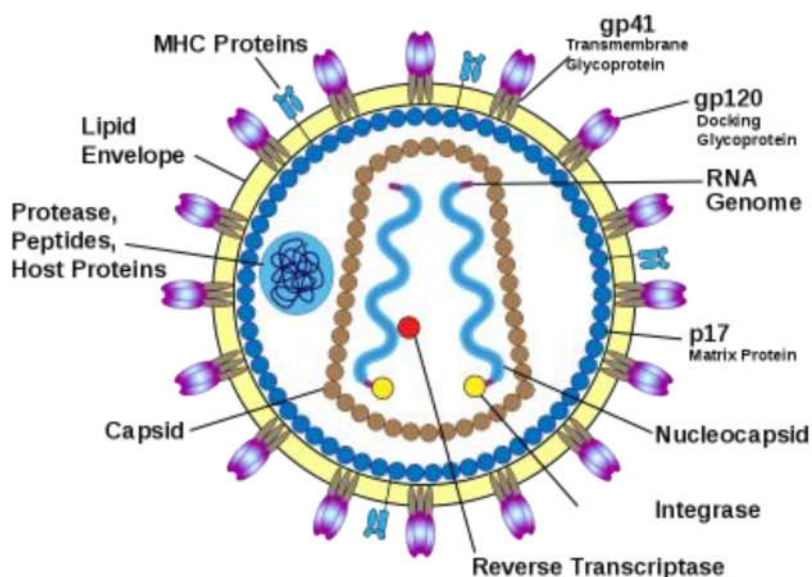


An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

HIV: the virus

Basics

- HIV is a RNA retrovirus of the lentivirus genus (lentiviruses are characterized by a long incubation period)
- two variants - HIV-1 and HIV-2
- HIV-2 is more common in west Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS



Basics structure

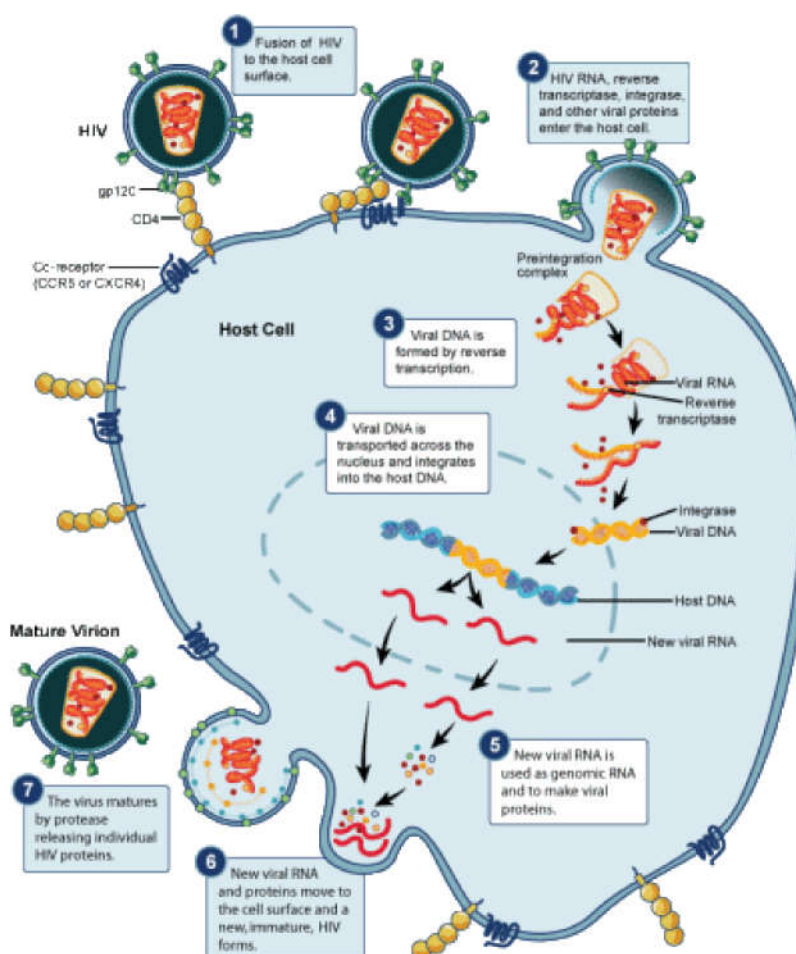
- spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24
- a matrix composed of viral protein p17 surrounds the capsid
- envelope proteins: gp120 and gp41
- pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease

Cell entry

- HIV can infect CD4 T cells, macrophages and dendritic cells
- gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages
- mutations in CCR5 can give immunity to HIV

Replication

- after entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

HLA associations

HLA antigens are encoded for by genes on chromosome 6. HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens. **Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:**

HLA-A3

- haemochromatosis

HLA-B5

- Behcet's disease

HLA-B27

- ankylosing spondylitis
- Reiter's syndrome
- acute anterior uveitis

HLA-DQ2/DQ8

- coeliac disease

HLA-DR2

- narcolepsy
- Goodpasture's

HLA-DR3

- dermatitis herpetiformis
- Sjogren's syndrome
- primary biliary cirrhosis

HLA-DR4

Hypercalcaemia: management

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

There is a limited role for the use of furosemide in hypercalcaemia. It may be useful in patients who cannot tolerate aggressive fluid rehydration

Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- **drugs***: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- metabolic acidosis
- Addison's
- rhabdomyolysis
- massive blood transfusion.

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

External Links:

[National Kidney Foundation/ British Dietetic Association](#)

Renal Diet

Hyponatraemia

Causes of hyponatraemia

- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus
- excess IV saline

Hyponatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death¹. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate¹.

1. Reynolds RM, Padfield PL, Seckl JR; Disorders of sodium balance. BMJ. 2006 Mar 25;332(7543):702-5.

Hypersensitivity

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

Type	Mechanism	Examples
Type I - Anaphylactic	Antigen reacts with IgE bound to mast cells	• Anaphylaxis • Atopy (e.g. asthma, eczema and hayfever)
Type II - Cell bound	IgG or IgM binds to antigen on cell surface	• Autoimmune haemolytic anaemia • ITP • Goodpasture's syndrome • Pernicious anaemia • Acute haemolytic transfusion reactions • Rheumatic fever • Pemphigus vulgaris / bullous pemphigoid
Type III - Immune complex	Free antigen and antibody (IgG, IgA) combine	• Serum sickness • Systemic lupus erythematosus • Post-streptococcal glomerulonephritis • Extrinsic allergic alveolitis (especially acute phase)
Type IV - Delayed hypersensitivity	T-cell mediated	• Tuberculosis / tuberculin skin reaction • Graft versus host disease • Allergic contact dermatitis • Scabies • Extrinsic allergic alveolitis (especially chronic phase) • Multiple sclerosis • Guillain-Barre syndrome

In recent times a further category has been added:

Type	Mechanism	Examples
Type V	Antibodies that recognise and bind to the cell surface receptors. This either stimulating them or blocking ligand binding	• Graves' disease • Myasthenia gravis

Hyperuricaemia

Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout

Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Increased synthesis

- Lesch-Nyhan disease
- myeloproliferative disorders
- diet rich in purines
- exercise
- psoriasis
- cytotoxics

Decreased excretion

- drugs: low-dose aspirin, diuretics, pyrazinamide
- pre-eclampsia
- alcohol
- renal failure
- lead

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

Hypocalcaemia: features

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

Hypokalaemia and acid-base balance

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis

- vomiting
- diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

Hyponatraemia

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolality levels aid making a diagnosis

Urinary sodium > 20 mmol/l

Sodium depletion, renal loss (patient often hypovolaemic):

- diuretics
- Addison's
- diuretic stage of renal failure

Patient often euvolaemic:

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

Urinary sodium < 20 mmol/l

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, cirrhosis
- reduced GFR: renal failure
- IV dextrose, psychogenic polydipsia

Hyponatraemia: correction

Central pontine myelinolysis

- demyelination syndrome caused by rapid correction of chronic hyponatraemia
- may lead to quadriparesis and bulbar palsy
- diagnosis: MRI brain

Hypophosphataemia

Causes

- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- refeeding syndrome
- primary hyperparathyroidism
- osteomalacia

Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

IL-1

Interleukin 1 (IL-1) is a key mediator of the immune response. It is secreted mainly by macrophages and monocytes and acts as a costimulator of T cell and B cell proliferation.

Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of vasoactive factors such as PAF, nitric oxide and prostacyclin it also causes vasodilation and increases vascular permeability. It is therefore one of the mediators of shock in sepsis. Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia.

Immune system cells: innate immune response

The following cells are mostly involved in the innate immune response:

Cell type	Functions and properties
Neutrophil	Primary phagocytic cell in acute inflammation Granules contain myeloperoxidase and lysozyme Most common type of white blood cell Multi-lobed nucleus
Basophil	Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface Bi-lobed nucleus
Mast cell	Present in tissues and are similar in function to basophils but derived from different cell lines Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface
Eosinophil	Defends against protozoan and helminthic infections Bi-lobed nucleus
Monocyte	Diffferentiates into macrophages Kidney shaped nucleus
Macrophage	Involved in phagocytosis of cellular debris and pathogens Acts as an antigen presenting cell Major source of IL-1
Natural killer cell	Induce apoptosis in virally infected and tumour cells
Dendritic cell	Acts as an antigen presenting cell

Immunoglobulins

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

Type	Frequency	Shape	Notes
IgG	75%	Monomer	• Enhance phagocytosis of bacteria and viruses • Fixes complement and passes to the fetal circulation • Most abundant isotype in blood serum
IgA	15%	Monomer/ dimer	• Found in secretions such as saliva, tears and mucous • Provides localized protection on mucous membranes • Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG) • Transported across the interior of the cell via transcytosis
IgM	10%	Pentamer	• First immunoglobulins to be secreted in response to an infection • Fixes complement but does not pass to the fetal circulation • Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) Pentamer when secreted
IgD	1%	Monomer	• Role in immune system largely unknown • Involved in activation of B cells.
IgE	0.1%	Monomer	• Mediates type 1 hypersensitivity reactions • Binds to Fc receptors found on the surface of mast cells and basophils • Provides immunity to parasites such as helminths • Least abundant isotype in blood serum

Immunoglobulins: therapeutics

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses

- primary and secondary immunodeficiency
- idiopathic thrombocytopenic purpura
- myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

Basics

- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

External Links

[Department of Health](#)

2011 Guidelines on the clinical use of immunoglobulins

Incidence and prevalence

These two terms are used to describe the frequency of a condition in a population.

The **incidence** is the number of new cases per population in a given time period.

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

The **prevalence** is the total number of cases per population at a particular point in time.

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship

- prevalence = incidence * duration of condition
- in chronic diseases the prevalence is much greater than the incidence
- in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Inherited metabolic disorders

Glycogen storage disease

Disorder	Deficient enzyme	Notes
Von Gierke's disease (type I)	Glucose-6-phosphatase	Hepatic glycogen accumulation. Key features include hypoglycaemia, lactic acidosis, hepatomegaly
Pompe's disease (type II)	Lysosomal alpha-1,4-glucosidase	Cardiac, hepatic and muscle glycogen accumulation. Key features include cardiomegaly
Cori disease (type III)	Alpha-1,6-glucosidase (debranching enzyme)	Hepatic, cardiac glycogen accumulation. Key features include muscle hypotonia
McArdle's disease (type V)	Glycogen phosphorylase	Skeletal muscle glycogen accumulation. Key features include myalgia, myoglobulinaemia with exercise

Lysosomal storage disease

Disorder	Defect	Notes
Gaucher's disease	Beta-glucocerebrosidase	Most common lipid storage disorder resulting in accumulation of glucocerebrosidase in the brain, liver and spleen. Key features include hepatosplenomegaly, aseptic necrosis of the femur
Tay-Sachs disease	Hexosaminidase A	Accumulation of GM ₂ ganglioside within lysosomes. Key features include developmental delay, cherry red spot on the macula, liver and spleen normal size (<i>cf.</i> Niemann-Pick)
Niemann-Pick disease	Sphingomyelinase	Key features include hepatosplenomegaly, cherry red spot on the macula
Fabry disease	Alpha-galactosidase-A	Accumulation of ceramide trihexoside. Key features include angiokeratomas, peripheral neuropathy of extremities, renal failure
Krabbe's disease	Galactocerebrosidase	Key features include peripheral neuropathy, optic atrophy, globoid cells
Metachromatic leukodystrophy	Arylsulfatase A	Demyelination of the central and peripheral nervous system

Mucopolysaccharidoses

Disorder	Defect	Notes
Hurler syndrome (type I)	Alpha-1-iduronidase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include gargoylism, hepatosplenomegaly, corneal clouding
Hunter syndrome (type II)	Iduronate sulfatase	Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include coarse facial features, behavioural problems/learning difficulties short stature, no corneal clouding

Intention to treat analysis

Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment

Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups

Iron metabolism

Absorption

- upper small intestine
- about 10% of dietary iron absorbed
- Fe^{2+} (ferrous iron) much better absorbed than Fe^{3+} (ferric iron)
- absorption is regulated according to body's need
- increased by vitamin C, gastric acid
- decreased by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)

Distribution in body

- total body iron = 4g
- haemoglobin = 70%
- ferritin and haemosiderin = 25%
- myoglobin = 4%
- plasma iron = 0.1%

Transport

- carried in plasma as Fe^{3+} bound to transferrin

Storage

- stored as ferritin in tissues

Excretion

- lost via intestinal tract following desquamation

Kallman's syndrome

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels

Diagnosis is by chromosomal analysis

Latex allergy

Sensitivity to latex may cause a number of problems:

- type I hypersensitivity (anaphylaxis)
- type IV hypersensitivity (allergic contact dermatitis)
- irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

Latex-fruit syndrome

It is recognised that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry.

Leukotrienes

Function

- mediators of inflammation and allergic reactions
- cause bronchoconstriction, mucous production
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

Production

- secreted by leukocytes
- formed from arachidonic acid by action of lipoxygenase
- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

Lower back pain

Lower back pain (LBP) is one of the most common presentations seen in practice. Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	May be acute or chronic Pain worse in the morning and on standing On examination there may be pain over the facets. The pain is typically worse on extension of the back
Spinal stenosis	Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
Ankylosing spondylitis	Typically a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases

External Links

[NICE](#)

2009 Low back pain: Early management of persistent non-specific low back pain

Lower back pain: prolapsed disc

A prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

Features

- leg pain usually worse than back
- pain often worse when sitting

The table below demonstrates the expected features according to the level of compression:

Site of compression	Features
L3 nerve root compression	Sensory loss over anterior thigh Weak quadriceps Reduced knee reflex Positive femoral stretch test
L4 nerve root compression	Sensory loss anterior aspect of knee Weak quadriceps Reduced knee reflex Positive femoral stretch test
L5 nerve root compression	Sensory loss dorsum of foot Weakness in foot and big toe dorsiflexion Reflexes intact Positive sciatic nerve stretch test
S1 nerve root compression	Sensory loss posterolateral aspect of leg and lateral aspect of foot Weakness in plantar flexion of foot Reduced ankle reflex Positive sciatic nerve stretch test

Management

- similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- if symptoms persist then referral for consideration of MRI is appropriate

External Links

[NICE Clinical Knowledge Summaries](#)

Sciatica guidelines

Lung cancer: referral

The 2015 NICE cancer referral guidelines gave the following advice:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:

- have chest x-ray findings that suggest lung cancer
- are aged 40 and over with unexplained haemoptysis

Offer an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:

- cough
- fatigue
- shortness of breath
- chest pain
- weight loss
- appetite loss

Consider an **urgent** chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

- persistent or recurrent chest infection
- finger clubbing
- supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- chest signs consistent with lung cancer
- thrombocytosis

External Links

[NICE](#)

2015 Lung cancer referral guidelines

Macroglossia

Causes

- hypothyroidism
- acromegaly
- amyloidosis
- Duchenne muscular dystrophy
- mucopolysaccharidosis (e.g. Hurler syndrome)

Patients with Down's syndrome are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

Marfan's syndrome

Marfan's syndrome is an autosomal dominant connective tissue disorder. It is caused by a defect in the fibrillin-1 gene on chromosome 15 and affects around 1 in 3,000 people.

Features

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- heart: dilation of the aortic sinuses (seen in 90%) which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%),
- lungs: repeated pneumothoraces
- eyes: upwards lens dislocation (superotemporal ectopia lentis), blue sclera, myopia
- dural ectasia (ballooning of the dural sac at the lumbosacral level)

♦The life expectancy of patients used to be around 40-50 years. With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years. Aortic dissection and other cardiovascular problems remain the leading cause of death however.

Membrane receptors

There are four main types of membrane receptor: ligand-gated ion channels, tyrosine kinase receptors, guanylate cyclase receptors and G protein-coupled receptors

Ligand-gated ion channel receptors

- generally mediate fast responses
- e.g. nicotinic acetylcholine, GABA-A & GABA-C, glutamate receptors

Tyrosine kinase receptors

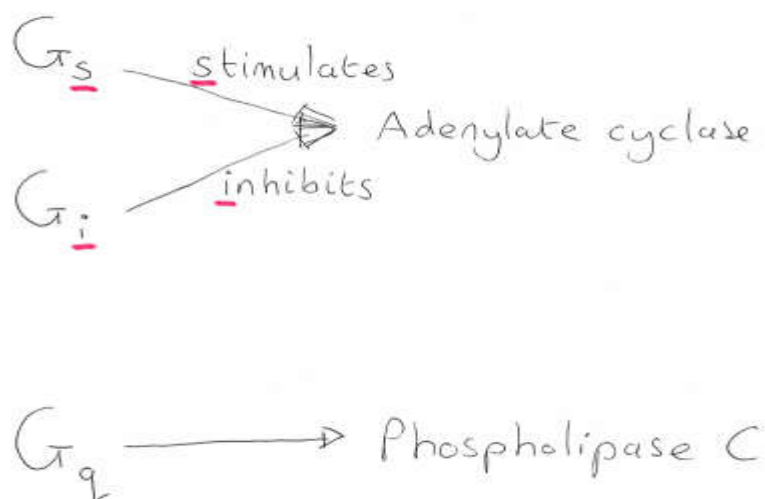
- intrinsic tyrosine kinase: insulin, insulin-like growth factor (IGF), epidermal growth factor (EGF)
- receptor-associated tyrosine kinase: growth hormone, prolactin, interferon, interleukin

Guanylate cyclase receptors

- contain intrinsic enzyme activity
- e.g. atrial natriuretic factor, brain natriuretic peptide

G protein-coupled receptors

- generally mediate slow transmission and affect metabolic processes
- activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light
- 7-helix membrane-spanning domains
- consist of 3 main subunits: alpha, beta and gamma
- the alpha subunit is linked to GDP. Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP, and the alpha subunit is activated
- G proteins are named according to the alpha subunit (G_s , G_i , G_q)



	G_s	G_i	G_q
Mechanism	Stimulates adenylate cyclase → increases cAMP → activates protein kinase A	Inhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A	Activates phospholipase C → splits PIP_2 to IP_3 & DAG → activates protein kinase C
Examples	• Beta-1 receptors (epinephrine, norepinephrine, dobutamine) • Beta-2 receptors (epinephrine, salbutamol) • H2 receptors (histamine) • D1 receptors (dopamine) • V2 receptors (vasopressin) • Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins	• M2 receptors (acetylcholine) • Alpha-2 receptors (epinephrine, norepinephrine) • D2 receptors (dopamine) • GABA-B receptor	• Alpha-1 receptors (epinephrine, norepinephrine) • H1 receptors (histamine) • V1 receptors (vasopressin) • M1, M3 receptors (acetylcholine)

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Days
Menstruation	1-4
Follicular phase (proliferative phase)	5-13
Ovulation	14
Luteal phase (secretory phase)	15-28

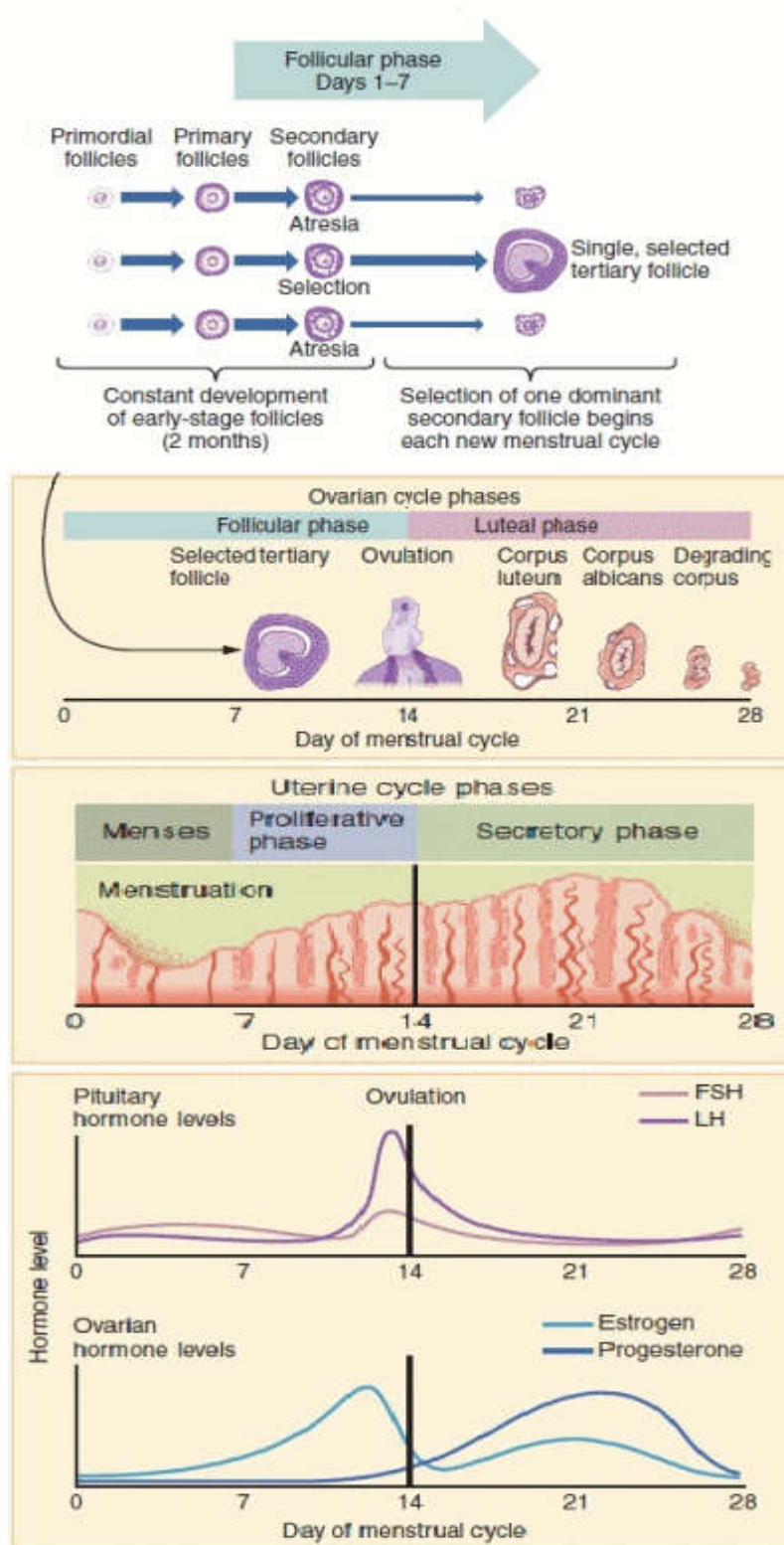


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/Menstrual_cycle)



Further details are given in the table below

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
Ovarian histology	A number of follicles develop. One follicle will become dominant around the mid-follicular phase	Corpus luteum
Endometrial histology	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
Hormones	A rise in FSH results in the development of follicles which in turn secrete oestradiol When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation	Progesterone secreted by corpus luteum rises through the luteal phase. If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall Oestradiol levels also rise again during the luteal phase
Cervical mucus	Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit	Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

External Links

[Wikipedia](#)

Menstrual cycle (including diagram).

Metabolic alkalosis

Metabolic alkalosis may be caused by a loss of hydrogen ions or a gain of bicarbonate. It is due mainly to problems of the kidney or gastrointestinal tract

Causes

- vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenosis, nasogastric suction)
- diuretics
- liquorice, carbenoxolone
- hypokalaemia
- primary hyperaldosteronism
- Cushing's syndrome
- Bartter's syndrome
- congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- aldosterone causes reabsorption of Na^+ in exchange for H^+ in the distal convoluted tubule
- ECF depletion (vomiting, diuretics) $\rightarrow$ Na^+ and Cl^- loss $\rightarrow$ activation of RAA system $\rightarrow$ raised aldosterone levels
- in hypokalaemia, K^+ shift from cells $\rightarrow$ ECF, alkalosis is caused by shift of H^+ into cells to maintain neutrality

Methaemoglobinaemia

Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe^{2+} to Fe^{3+} . This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe^{3+} cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO_2 but decreased oxygen saturation

Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

Mitochondrial diseases

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

Histology

- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

External Links

[Royal College of Physicians](#)

2013 How to spot mitochondrial disease in adults

Molecular biology techniques

The following table shows a very basic summary of molecular biology techniques

Technique	Description
Southern blotting	Detects DNA
Northern blotting	Detects RNA
Western blotting	Detects proteins Uses gel electrophoresis to separate native proteins by 3-D structure Examples include the confirmatory HIV test

Molecular biology techniques

- SNOW (**S**outh - **N**Orth - **W**est)
- DROP (**D**NA - **R**NA - **P**rotein)

Enzyme-linked immunosorbent assay (ELISA)

- a type of biochemical assay used to detect antigens and antibodies
- a colour changing enzyme is attached to the antibody if looking for an antigen and to an antigen if looking for an antibody
- the sample therefore changes colour if the antigen or antibody is detected
- an example includes the **initial** HIV test.

Monoclonal antibodies

Monoclonal antibodies have an increasing role in medicine. They are manufactured by a technique called somatic cell hybridization. This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies. The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from a human antibody.

Clinical examples of monoclonal antibodies:

- infliximab (anti-TNF): used in rheumatoid arthritis and Crohn's
- rituximab (anti-CD20): used in non-Hodgkin's lymphoma and rheumatoid arthritis
- cetuximab (epidermal growth factor receptor antagonist): used in metastatic colorectal cancer and head and neck cancer
- trastuzumab (HER2/neu receptor antagonist): used in metastatic breast cancer
- alemtuzumab (anti-CD52): used in chronic lymphocytic leukaemia
- abciximab (glycoprotein IIb/IIIa receptor antagonist): prevention of ischaemic events in patients undergoing percutaneous coronary interventions
- OKT3 (anti-CD3): used to prevent organ rejection

Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- diagnosis of viral infections

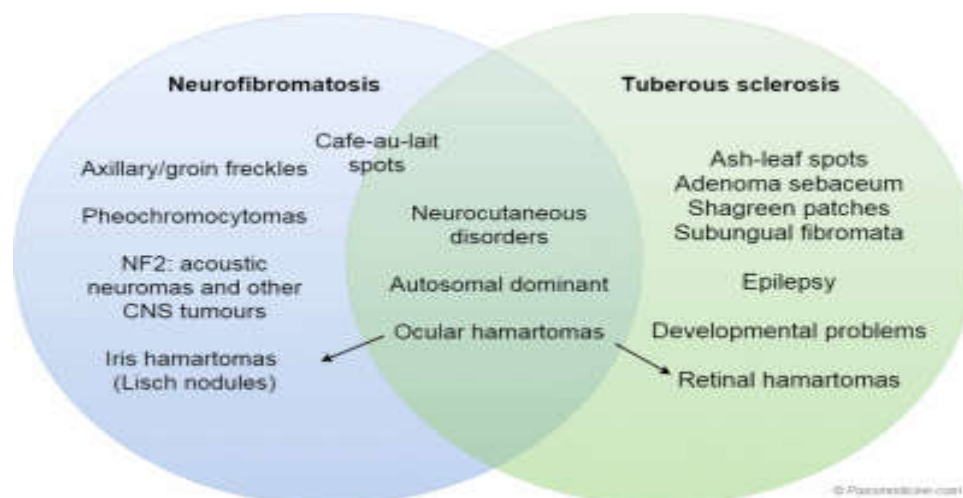
Neurofibromatosis

There are two types of neurofibromatosis, NF1 and NF2. Both are inherited in an autosomal dominant fashion. NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on chromosome 17 which encodes neurofibromin and affects around 1 in 4,000.

NF2 is caused by gene mutation on chromosome 22 and affects around 1 in 100,000.

Features

NF1	NF2
Café-au-lait spots (≥ 6 , 15 mm in diameter) Axillary/groin freckles Peripheral neurofibromas Iris hamatomas (Lisch nodules) in $> 90\%$ Scoliosis Pheochromocytomas	Bilateral acoustic neuromas Multiple intracranial schwannomas, meningiomas and ependymomas



Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise.

External Links

[National Center for Biotechnology Information](#)

Guidelines for the diagnosis and management of individuals with neurofibromatosis 1

Nitric oxide

Previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes. It is formed from L-arginine and oxygen by nitric oxide synthetase (NOS). An inducible form of NOS has been shown to be present in macrophages. Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals

Effects

- acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca^{2+} levels
- vasodilation, mainly venodilation
- inhibits platelet aggregation

Clinical relevance

- underproduction of NO is implicated in hypertrophic pyloric stenosis
- lack of NO is thought to promote atherosclerosis
- in sepsis increased levels of NO contribute to septic shock
- organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure)
- sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions

Noonan's syndrome

Often thought of as the 'male Turner's', Noonan's syndrome is an autosomal dominant condition associated with a normal karyotype. It is thought to be caused by a defect in a gene on chromosome 12

As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:

- cardiac: pulmonary valve stenosis
- ptosis
- triangular-shaped face
- low-set ears
- coagulation problems: factor XI deficiency

Normal distribution

The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements

Properties of the Normal distribution

- symmetrical i.e. Mean = mode = median
- 68.3% of values lie within 1 SD of the mean
- 95.4% of values lie within 2 SD of the mean
- 99.7% of values lie within 3 SD of the mean
- this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- the range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

Standard deviation

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- SD = square root (variance)

Numbers needed to treat and absolute risk reduction

Numbers needed to treat (NNT) is a measure that indicates how many patients would require an intervention to reduce the expected number of outcomes by one

It is calculated by $1/(\text{Absolute risk reduction})$ and is rounded to the next highest whole number

Experimental event rate (EER) = (Number who had particular outcome with the intervention) / (Total number who had the intervention)

Control event rate (CER) = (Number who had particular outcome with the control/ (Total number who had the control)

Absolute risk reduction = CER-EER or EER-CER?

The absolute risk reduction (ARR) may be calculated by finding the absolute difference between the control event rate (CER) and the experimental event rate (EER). You will often find both versions of the above listed in different sources. In some ways it doesn't matter which you use as you will end up with the same answer but from a technical point of view:

- if the outcome of the study is undesirable then $ARR = CER - EER$
- if the outcome of the study is desirable then $ARR^* = EER - CER$

*this may be more accurately termed absolute benefit increase, rather than absolute risk reduction

External Links

[Centre for Evidence-Based Medicine](#)

Number Needed to Treat (NNT)

Obesity: physiology**Leptin**

Leptin is thought to play a key role in the regulation of body weight. It is produced by adipose tissue and acts on satiety centres in the hypothalamus and decreases appetite. More adipose tissue (e.g. in obesity) results in high leptin levels.

Leptin stimulates the release of melanocyte-stimulating hormone (MSH) and corticotrophin-releasing hormone (CRH). Low levels of leptin stimulates the release of neuropeptide Y (NPY)

Ghrelin

Where as leptin induces satiety, ghrelin stimulates hunger. It is produced mainly by the P/D1 cells lining the fundus of the stomach and epsilon cells of the pancreas. Ghrelin levels increase before meals and decrease after meals

Odds and odds ratio

Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome. The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

Odds vs. probability

In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- the probability of rolling a six is $1/6$ or 0.166666
- the odds of rolling a six is $1/5$ or 0.2

Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

The odds of achieving significant pain relief with paracetamol = $40 / 20 = 2$

The odds of achieving significant pain relief with placebo = $30 / 60 = 0.5$

Therefore the odds ratio = $2 / 0.5 = 4$.

External Links

[Cochrane](#)

Difference between odds and risk

Osteogenesis imperfecta

Osteogenesis imperfecta (more commonly known as brittle bone disease) is a group of disorders of collagen metabolism resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1

Overview

- autosomal dominant
- abnormality in type 1 collagen due to decreased synthesis of pro-alpha 1 or pro-alpha 2 collagen polypeptides

Features

- presents in childhood
- fractures following minor trauma
- blue sclera
- deafness secondary to otosclerosis
- dental imperfections are common

Osteomalacia

Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

Types

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)

Treatment

- calcium with vitamin D tablets

Oxygen dissociation curve

The oxygen dissociation curve describes the relationship between the percentage of saturated haemoglobin and partial pressure of oxygen in the blood. It is not affected by haemoglobin concentration

Basics

- shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. decreased oxygen delivery to tissues
- shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. enhanced oxygen delivery to tissues

Shifts to Left = Lower oxygen delivery	Shifts to Right = Raised oxygen delivery
HbF, methaemoglobin, carboxyhaemoglobin Low [H ⁺] (alkali) Low pCO ₂ Low 2,3-DPG Low temperature	Raised [H ⁺] (acidic) Raised pCO ₂ Raised 2,3-DPG* Raised temperature

The L rule

Shifts to **L** → Lower oxygen delivery, caused by

- Low [H⁺] (alkali)
- Low pCO₂
- Low 2,3-DPG
- Low temperature

Another mnemonic is 'CADET, face Right!' for CO₂, Acid, 2,3-DPG, Exercise and Temperature

*2,3-diphosphoglycerate

p53

p53 is a tumour suppressor gene located on chromosome 17p. It is the most commonly mutated gene in breast, colon and lung cancer

p53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of apoptosis

Li-Fraumeni syndrome is a rare autosomal dominant disorder characterised by the early onset of a variety of cancers such as sarcomas and breast cancer. It is caused by mutation in the p53 gene

PCR

Polymerase chain reaction (PCR) is a molecular genetic investigation technique. The main advantage of PCR is its sensitivity: only one strand of sample DNA is needed to detect a particular DNA sequence. It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics. Prior to the procedure it is necessary to have two DNA oligonucleotide primers. These are complimentary to specific DNA sequences at either end of the target DNA

Initial prep

- sample of DNA is added to test tube along with two DNA primers
- a thermostable DNA polymerase (Taq) is added

The following cycle then takes place

- mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA
- mixture is allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially

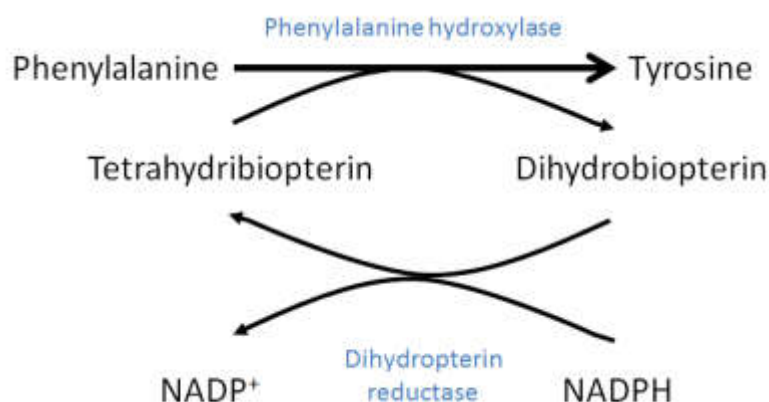
The above cycle is then repeated, with the amount of DNA doubling each time

Reverse transcriptase PCR

- used to amplify RNA
- RNA is converted to DNA by reverse transcriptase
- gene expression in the form of mRNA (rather than the actual DNA sequence) can therefore be analyzed

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine. In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is around 1 in 10,000 live births.



Features

- usually presents by 6 months e.g. with developmental delay
- child classically has fair hair and blue eyes
- learning difficulties
- seizures, typically infantile spasms
- eczema
- 'musty' odour to urine and sweat*

Diagnosis

- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

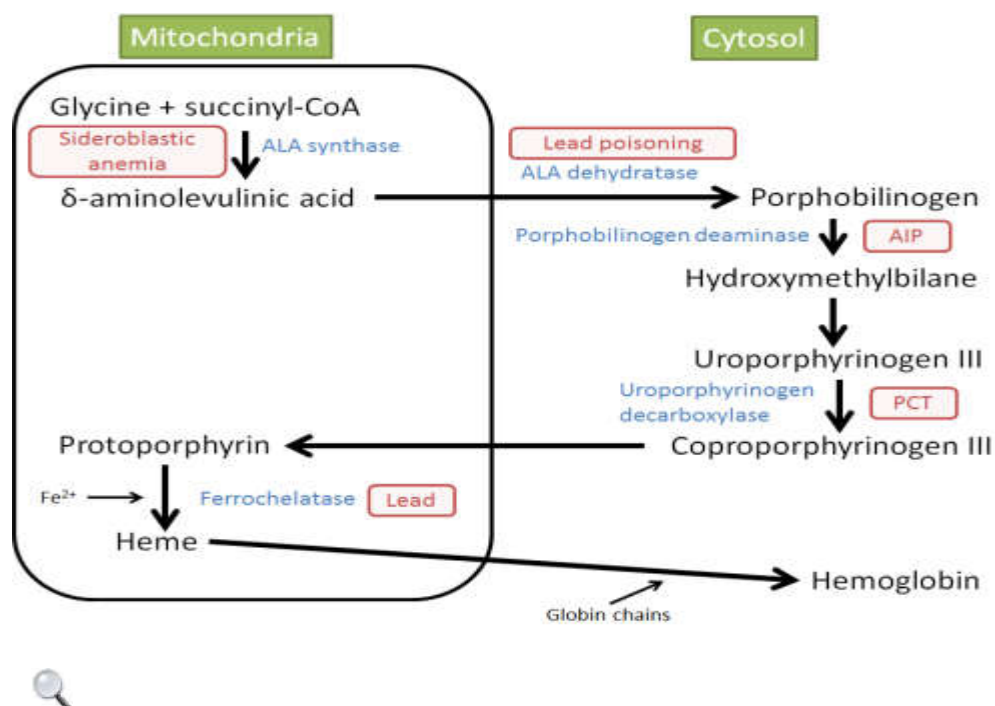
- poor evidence base to suggest strict diet prevents learning disabilities
- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

*secondary to phenylacetate, a phenylketone

Porphyrias

Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute



Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a form of nuclear imaging which uses fluorodeoxyglucose (FDG) as the radiotracer. This allows a 3D image of metabolic activity to be generated using glucose uptake as a proxy marker. The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

Uses

- evaluating primary and possible metastatic disease
 - cardiac PET: not used mainstream currently
-

Prader-Willi syndrome

Prader-Willi syndrome is an example of genetic imprinting where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:

- Prader-Willi syndrome if gene deleted from father
- Angelman syndrome if gene deleted from mother

Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15. **This may be due to:**

- microdeletion of paternal 15q11-13 (70% of cases)
- maternal uniparental disomy of chromosome 15

Features

- hypotonia during infancy
 - dysmorphic features
 - short stature
 - hypogonadism and infertility
 - learning difficulties
 - childhood obesity
 - behavioural problems in adolescence
-

Pre- and post- test odds and probability

Pre-test probability

The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence)

For example, the prevalence of rheumatoid arthritis in the UK is 1%

Post-test probability

The proportion of patients with that particular test result who have the target disorder

Post-test probability = post test odds / (1 + post-test odds)

Pre-test odds

The odds that the patient has the target disorder before the test is carried out

Pre-test odds = pre-test probability / (1 - pre-test probability)

Post-test odds

The odds that the patient has the target disorder after the test is carried out

Post-test odds = pre-test odds x likelihood ratio

where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

Pre-eclampsia

Pre-eclampsia is a condition seen after 20 weeks gestation characterised by pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours). Oedema used to be third element of the classic triad but is now often not included in the definition as it is not specific

Pre-eclampsia is important as it predisposes to the following problems:

- fetal: prematurity, intrauterine growth retardation
- eclampsia
- haemorrhage: placental abruption, intra-abdominal, intra-cerebral
- cardiac failure
- multi-organ failure

Risk factors

- > 40 years old
- nulliparity (or new partner)
- multiple pregnancy
- body mass index > 30 kg/m²
- diabetes mellitus
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- previous history of pre-eclampsia
- pre-existing vascular disease such as hypertension or renal disease

Features of severe pre-eclampsia

- hypertension: typically > 170/110 mmHg and proteinuria as above
- proteinuria: dipstick ++/+++
- headache
- visual disturbance
- papilloedema
- RUQ/epigastric pain
- hyperreflexia
- platelet count < 100 * 10⁶/l, abnormal liver enzymes or HELLP syndrome

Management

- consensus guidelines recommend treating blood pressure > 160/110 mmHg although many clinicians have a lower threshold
- oral labetalol is now first-line following the 2010 NICE guidelines. Nifedipine and hydralazine may also be used
- delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario

External Links

[NICE](#)

2010 Hypertension in pregnancy

Prediabetes and impaired glucose regulation

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

Terminology

- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

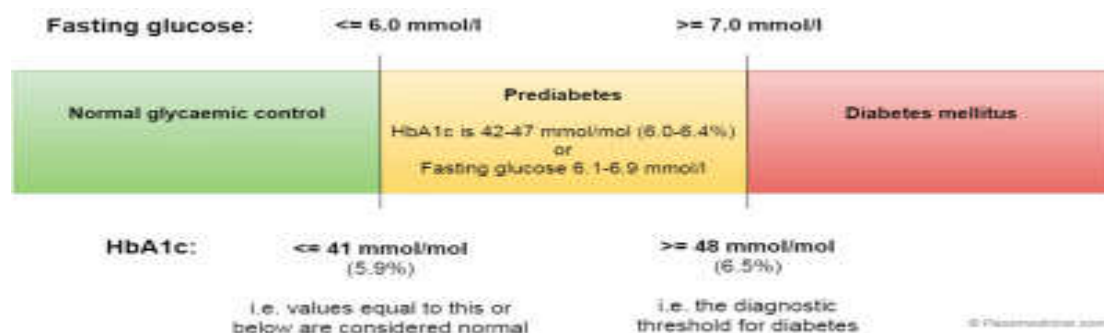


Diagram showing the spectrum of diabetes diagnosis

Management

- lifestyle modification: weight loss, increased exercise, change in diet
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk '*whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme*'

Impaired fasting glucose and impaired glucose tolerance

There are two main types of IGR:

- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions

- a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- people with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT

External Links

[NICE](#)

2012 Preventing type 2 diabetes guidelines

[Diabetes UK](#)

Prediabetes.

Premature ovarian failure

Premature ovarian failure is defined as the onset of menopausal symptoms and elevated gonadotrophin levels before the age of 40 years. It occurs in around 1 in 100 women.

Causes

- idiopathic - the most common cause
- chemotherapy
- autoimmune
- radiation

Features are similar to those of the normal climacteric but the actual presenting problem may differ

- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- raised FSH, LH levels

External Links

[Guys & St Thomas NHS](#)

Premature ovarian failure information sheet

Progestogen only pill: advantages/disadvantages

Advantages

- highly effective (failure rate = 1 per 100 woman years)
- doesn't interfere with sex
- contraceptive effects reversible upon stopping
- can be used whilst breast-feeding
- can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

Disadvantages

- irregular periods: some users may not have periods whilst others may have irregular or light periods. This is the most common adverse effect
- doesn't protect against sexually transmitted infections
- increased incidence of functional ovarian cysts
- common side-effects include breast tenderness, weight gain, acne and headaches. These symptoms generally subside after the first few months

External Links

[Faculty of Sexual and Reproductive Healthcare](#)

2009 POP guidelines

Prolactin and galactorrhoea

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines
- haloperidol
- very rare: SSRIs, opioids

External Links

[Patient.info](#)

Galactorrhoea review

Pseudohypoparathyroidism

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism there is a complete receptor defect whereas in type II the cell receptor is intact. Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion*

Bloods

- PTH: high
- calcium: low
- phosphate: high

Features

- short fourth and fifth metacarpals
- short stature
- cognitive impairment
- obesity
- round face

Investigation

- infusion of PTH followed by measurement of urinary phosphate and cAMP measurement - this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

*it was previously thought to be an X-linked dominant condition

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive*) characterised by an abnormality in elastic fibres

Features

- retinal angioid streaks
- 'plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae
- cardiac: mitral valve prolapse, increased risk of ischaemic heart disease
- gastrointestinal haemorrhage

*there are reports of autosomal dominant inheritance in a minority of cases

Pulmonary capillary wedge pressure

●Pulmonary capillary wedge pressure (PCWP) is measured using a balloon tipped Swan-Ganz catheter which is inserted into the pulmonary artery. The pressure measured is similar to that of the left atrium (normally 6-12 mmHg).

●One of the main uses of measuring the PCWP is determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome.

●In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

Pulmonary surfactant

Surfactant is a mixture of phospholipids, carbohydrates and proteins released by type 2 pneumocytes. The main functioning component is dipalmitoyl phosphatidylcholine (DPPC) which reduces alveolar surface tension.

Basics

- first detectable around 28 weeks
 - as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
 - reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)
 - lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration
-

Radial nerve

Overview

- arises from the posterior cord of the brachial plexus (C5-8)

Motor to

- extensor muscles (forearm, wrist, fingers, thumb)

Sensory to

- dorsal aspect of lateral 3 1/2 fingers
- however, only small area between the dorsal aspect of the 1st and 2nd metacarpals is unique to the radial nerve

Patterns of damage

- wrist drop
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- paralysis of triceps.

Ramsay Hunt syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is caused by the reactivation of the varicella zoster virus in the geniculate ganglion of the seventh cranial nerve.

Features

- auricular pain is often the first feature
- facial nerve palsy
- vesicular rash around the ear
- other features include vertigo and tinnitus

Management

- oral aciclovir and corticosteroids are usually given

Relative risk

Relative risk (RR) is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER). The term relative risk ratio is sometimes used instead of relative risk.

To recap

- EER = rate at which events occur in the experimental group
- CER = rate at which events occur in the control group

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Experienced significant pain relief
Paracetamol	100	60
Placebo	80	20

Experimental event rate, $EER = 60 / 100 = 0.6$

Control event rate, $CER = 20 / 80 = 0.25$

Therefore the relative risk ratio = $EER / CER = 0.6 / 0.25 = 2.4$

Chapter: clinical science

◆If the risk ratio is > 1 then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls. It is therefore appropriate to calculate the relative risk increase if necessary (see below).

◆If the risk ratio is ≤ 1 then the rate of an event is decreased compared to controls. The relative risk reduction should therefore be calculated (see below).

Relative risk reduction (RRR) or relative risk increase (RRI) is calculated by dividing the absolute risk change by the control event rate

Using the above data, $RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140\%$

Renal anatomy

The tables below show the anatomical relations of the kidneys:

Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland	Liver
Duodenum	Distal part of small intestine
Colon	

Left kidney

Direct contact	Layer of peritoneum in-between
Left suprarenal gland	Stomach
Pancreas	Spleen
Colon	Distal part of small intestine

Renal transplant: HLA typing and graft failure

The human leucocyte antigen (HLA) system is the name given to the major histocompatibility complex (MHC) in humans. It is coded for on chromosome 6.

Some basic points on the HLA system

- class 1 antigens include A, B and C. Class 2 antigens include DP,DQ and DR
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows
 $DR > B > A$

Graft survival

- 1 year = 90%, 10 years = 60% for cadaveric transplants
- 1 year = 95%, 10 years = 70% for living-donor transplants

Post-op problems

- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

Hyperacute acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction)
- rarely seen due to HLA matching

Acute graft failure (< 6 months)

- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
- may be reversible with steroids and immunosuppressants

Causes of chronic graft failure (> 6 months)

- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- recurrence of original renal disease (MCGN > IgA > FSGS)

Renin

Renin is secreted by juxtaglomerular cells and hydrolyses angiotensinogen to produce angiotensin I

Factors stimulating renin secretion:

- hypotension causing reduced renal perfusion
- hyponatraemia
- sympathetic nerve stimulation
- catecholamines
- erect posture

Factors reducing renin secretion:

- drugs: beta-blockers, NSAIDs

Renin-angiotensin-aldosterone system

Adrenal cortex (mnemonic **GFR - ACD**)

- zona **g**lomerulosa (on outside): mineralocorticoids, mainly **a**ldosterone
- zona **f**asciculata (middle): glucocorticoids, mainly **c**ortisol
- zona **r**eticularis (on inside): androgens, mainly **d**ehydroepiandrosterone (DHEA)

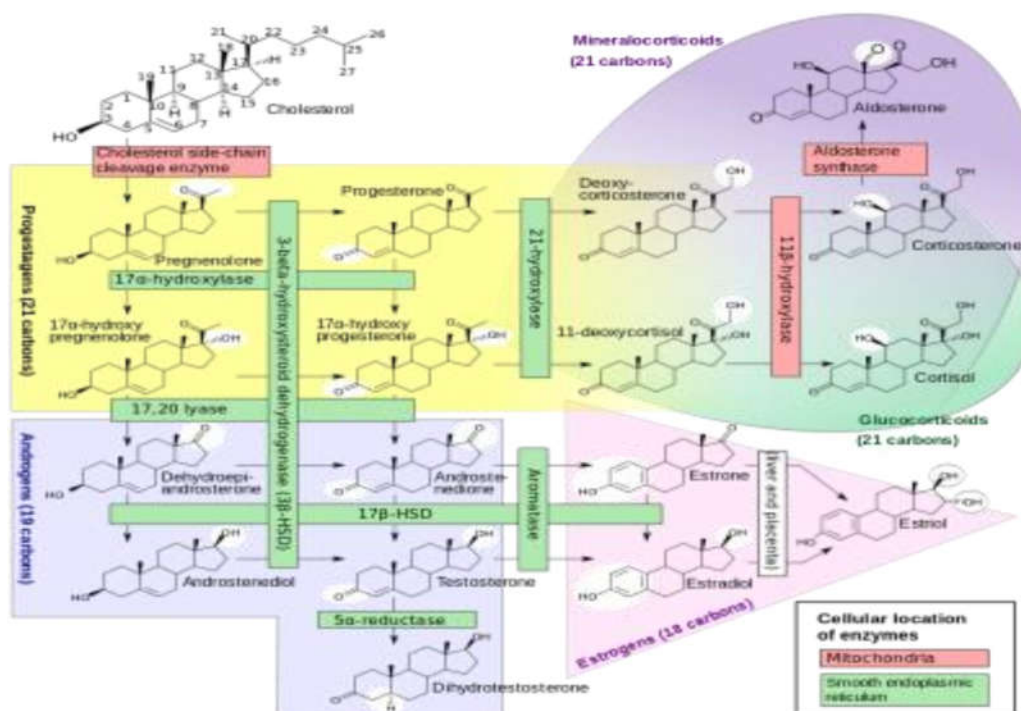


Image sourced from [Wikipedia](#)

Renin

- an enzyme that is **released by the renal juxtaglomerular cells in response to reduced renal perfusion**
- other factors that stimulate renin secretion include hyponatraemia, sympathetic nerve stimulation
- hydrolyses angiotensinogen to form angiotensin I

Angiotensin II

- angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I $\rightarrow$ angiotensin II
- angiotensin II has a wide variety of actions:
- causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** $\rightarrow$ increased filtration fraction (FF) to preserve GFR. Remember that $FF = GFR / \text{renal plasma flow}$
- **stimulates thirst** (via the hypothalamus)
- **stimulates aldosterone and ADH** release
- **increases proximal tubule Na^+/H^+ activity**

Aldosterone

- released by the zona glomerulosa in response to raised **angiotensin II, potassium, and ACTH levels**
- **causes retention of Na^+** in exchange for K^+/H^+ in distal tubule

Respiratory physiology

Chloride shift

- CO_2 diffuses into RBCs
- $\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{carbonic anhydrase}} \text{HCO}_3^- + \text{H}^+$
- H^+ combines with Hb
- HCO_3^- diffuses out of cell, Cl^- replaces it

Bohr effect

- increasing acidity (or pCO_2) means O_2 binds less well to Hb

Haldane effect

- increase pO_2 means CO_2 binds less well to Hb

Respiratory physiology: control

Control of respiration

- central regulatory centres
 - central and peripheral chemoreceptors
 - pulmonary receptors
- Central regulatory centres**

- medullary respiratory centre
- apneustic centre (lower pons)
- pneumotaxic centre (upper pons)

Central and peripheral chemoreceptors

- central: raised $[H^+]$ in ECF stimulates respiration
- peripheral: carotid + aortic bodies, respond to raised pCO_2 & $[H^+]$, lesser extent low pO_2

Pulmonary receptors

- stretch receptors, lung distension causes slowing of respiratory rate (Hering-Breuer reflex)
 - irritant receptor, leading to bronchoconstriction
 - juxtacapillary receptors, stimulated by stretching of the microvasculature
-

Respiratory physiology: hypoxia

A fall in the partial pressure of oxygen in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be diverted to better aerated areas of the lung and improves the efficiency of gaseous exchange

Respiratory physiology: lung compliance

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of increased compliance

- age
- emphysema - this is due to loss alveolar walls and associated elastic tissue

Causes of decreased compliance

- pulmonary oedema
 - pulmonary fibrosis
 - pneumonectomy
 - kyphosis
-

Respiratory physiology: lung volumes

The diagram below demonstrates the lung volumes which may be measured:

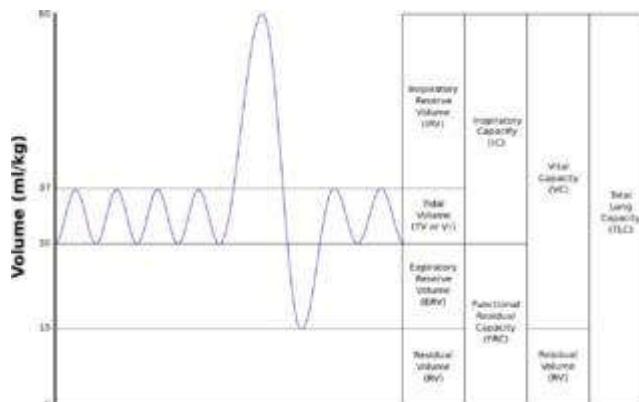


Image sourced from [Wikipedia](#)



Tidal volume (TV)

- volume inspired or expired with each breath at rest
- 500ml in males, 350ml in females

Inspiratory reserve volume (IRV) = 2-3 L

- maximum volume of air that can be inspired at the end of a normal tidal inspiration
- inspiratory capacity = TV + IRV

Expiratory reserve volume (ERV) = 750ml

- maximum volume of air that can be expired at the end of a normal tidal expiration

Residual volume (RV) = 1.2L

- volume of air remaining after maximal expiration
- increases with age
- $RV = FRC - ERV$

Vital capacity (VC) = 5L

- maximum volume of air that can be expired after a maximal inspiration
- 4,500ml in males, 3,500 mls in females
- decreases with age
- $VC = \text{inspiratory capacity} + ERV$

Total lung capacity (TLC) is the sum of the vital capacity + residual volume

Physiological dead space (V_D)

- $V_D = \text{tidal volume} * (PaCO_2 - PeCO_2) / PaCO_2$
- where $PeCO_2$ = expired air CO_2

Screening test statistics

Patients and doctors need to know if a disease or condition is present or absent. Tests can be used to help us decide. Tests generally guide us by indicating how likely it is that the patient has the condition.

In order to interpret test results we need to have a working knowledge of the statistics used to describe them.

Contingency tables (also known as 2 * 2 tables, see below) are used to illustrate and calculate test statistics such as sensitivity. It would be unusual for a medical exam not to feature a question based around screening test statistics. Commit the following table to memory and spend time practicing using it as you will be expected to make calculations using it in your exam.

TP = true positive; FP = false positive; TN = true negative; FN = false negative

	Disease present	Disease absent
Test positive	TP	FP
Test negative	FN	TN

The table below lists the main statistical terms used in relation to screening tests:

Measure	Formula	Plain english
Sensitivity	$TP / (TP + FN)$	Proportion of patients with the condition who have a positive test result
Specificity	$TN / (TN + FP)$	Proportion of patients without the condition who have a negative test result
Positive predictive value	$TP / (TP + FP)$	The chance that the patient has the condition if the diagnostic test is positive
Negative predictive value	$TN / (TN + FN)$	The chance that the patient does not have the condition if the diagnostic test is negative
Likelihood ratio for a positive test result	$\text{sensitivity} / (1 - \text{specificity})$	How much the odds of the disease increase when a test is positive
Likelihood ratio for a negative test result	$(1 - \text{sensitivity}) / \text{specificity}$	How much the odds of the disease decrease when a test is negative

Positive and negative predictive values are prevalence dependent. Likelihood ratios are not prevalence dependent.

Precision

The precision quantifies a tests ability to produce the same measurements with repeated tests.

Screening: Wilson and Junger criteria

1. The condition should be an important public health problem
2. There should be an acceptable treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. The natural history of the condition, including its development from latent to declared disease should be adequately understood
6. There should be a suitable test or examination
7. The test or examination should be acceptable to the population
8. There should be agreed policy on whom to treat
9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
10. Case-finding should be a continuous process and not a 'once and for all' project

External Links

Patient.co.uk

Screening programmes in the UK

Second messengers

Overview

- many different types
- allow amplification of external stimulus

	cAMP system	Phosphoinositol system	cGMP system	Tyrosine kinase system
Ligand: Neurotransmitters (Receptor)	Epinephrine (α_2 , β_1 , β_2) Acetylcholine (M2)	Epinephrine (α_1) Acetylcholine (M1, M3)	-	-
Ligand: Hormones	ACTH, ADH, calcitonin, FSH, glucagon, hCG, LH, MSH, PTH, TSH, GHRH*	angiotensin II, GnRH, GHRH*, Oxytocin, TRH	ANP, Nitric oxide	insulin, growth hormone, IGF, PDGF
Primary effector	Adenyl cyclase	Phospholipase C	Guanylate cyclase	Receptor tyrosine kinase
Secondary messenger	cAMP (cyclic adenosine monophosphate)	IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol)	cGMP	Protein phosphatase

*the cAMP pathway is the most important

SIADH: causes

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

Causes of SIADH

Category	Examples
Malignancy	• small cell lung cancer • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas • SSRIs, tricyclics • carbamazepine • vincristine • cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

Significance tests

A null hypothesis (H_0) states that two treatments are equally effective (and is hence negatively phrased). A significance test uses the sample data to assess how likely the null hypothesis is to be correct.

For example:

- 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis (H_1) is the opposite of the null hypothesis, i.e. There is a difference between the two treatments

The **p value** is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. It is therefore equal to the chance of making a type I error (see below).

Two types of errors may occur when testing the null hypothesis:

- type I: the null hypothesis is rejected when it is true - i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance.
- type II: the null hypothesis is accepted when it is false - i.e. Failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha

	Study accepts H_0	Study rejects H_0
Reality H_0		Type 1 error (alpha)
Reality H_1	Type 2 error (beta)	Power (1 - beta)

The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference

- power = 1 - the probability of a type II error
- power can be increased by increasing the sample size

Significance tests: types

The type of significance test used depends on whether the data is parametric (something which can be measured, usually normally distributed) or non-parametric

Parametric tests

- Student's t-test - paired or unpaired*
- Pearson's product-moment coefficient - correlation

Non-parametric tests

- Mann-Whitney U test - unpaired data
- Wilcoxon signed-rank test - compares two sets of observations on a single sample
- chi-squared test - used to compare proportions or percentages
- Spearman, Kendall rank - correlation

*paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

Skewed distributions

Normal (Gaussian) distributions: mean = median = mode

Positively skewed distribution: mean > median > mode

Negatively skewed distribution mean < median < mode

To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'

SLE: features

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder. It typically presents in early adulthood and is more common in women and people of Afro-Caribbean origin.

General features

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin

- malar (butterfly) rash: spares nasolabial folds
- discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- arthralgia
- non-erosive arthritis

Cardiovascular

- myocarditis

Respiratory

- pleurisy
- fibrosing alveolitis

Chapter: clinical science

Renal

- proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

Splenomegaly

Massive splenomegaly

- myelofibrosis
- chronic myeloid leukaemia
- visceral leishmaniasis (kala-azar)
- malaria
- Gaucher's syndrome

Other causes (as above plus)

- portal hypertension e.g. secondary to cirrhosis
- lymphoproliferative disease e.g. CLL, Hodgkin's
- haemolytic anaemia
- infection: hepatitis, glandular fever
- infective endocarditis
- sickle-cell*, thalassaemia
- rheumatoid arthritis (Felty's syndrome)

*the majority of adults patients with sickle-cell will have an atrophied spleen due to repeated infarction

Stevens-Johnson syndrome

Stevens-Johnson syndrome severe form of erythema multiforme associated with mucosal involvement and systemic symptoms

Features

- rash is typically maculopapular with target lesions being characteristic. May develop into vesicles or bullae
- mucosal involvement
- systemic symptoms: fever, arthralgia



© Image used on license from [DermNet NZ](https://www.dermnetnz.org/)



Causes

- idiopathic
- bacteria: *Mycoplasma*, *Streptococcus*
- viruses: herpes simplex virus, Orf
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill
- connective tissue disease e.g. SLE
- sarcoidosis
- malignancy

Study design

The following table highlights the main features of the main types of study:

Study type	Key features
Randomised controlled trial	Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) Practical or ethical problems may limit use
Cohort study	Observational and prospective. Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. The usual outcome measure is the relative risk. Examples include Framingham Heart Study
Case-control study	Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition. The usual outcome measure is the odds ratio. Inexpensive, produce quick results Useful for studying rare conditions Prone to confounding
Cross-sectional survey	Provide a 'snapshot', sometimes called prevalence studies Provide weak evidence of cause and effect

Study design: evidence and recommendations

Levels of evidence

- Ia - evidence from meta-analysis of randomised controlled trials
- Ib - evidence from at least one randomised controlled trial
- IIa - evidence from at least one well designed controlled trial which is not randomised
- IIb - evidence from at least one well designed experimental trial
- III - evidence from case, correlation and comparative studies
- IV - evidence from a panel of experts

Grading of recommendation

- Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
- Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- Grade C - based on evidence from a panel of experts (i.e. IV)

Study design: new drugs

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- **superiority:** whilst this may seem the natural aim of a trial one problem is the large sample size needed to show a significant benefit over an existing treatment
- **equivalence:** an equivalence margin is defined ($-\delta$ to $+\delta$) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect
- **non-inferiority:** similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. $-\delta$). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

External Links

[European Medicines Agency](#)

Further information on trial design

T-Helper cells

There are two major subsets of T-Helper cells:

Th1

- involved in the cell mediated response and delayed (type IV) hypersensitivity
- secrete IFN-gamma, IL-2, IL-3

Th2

- involved in mediating humoral (antibody) immunity
- e.g. stimulating production of IgE in asthma
- secrete IL-4, IL-5, IL-6, IL-10, IL-13

Thiazide diuretics

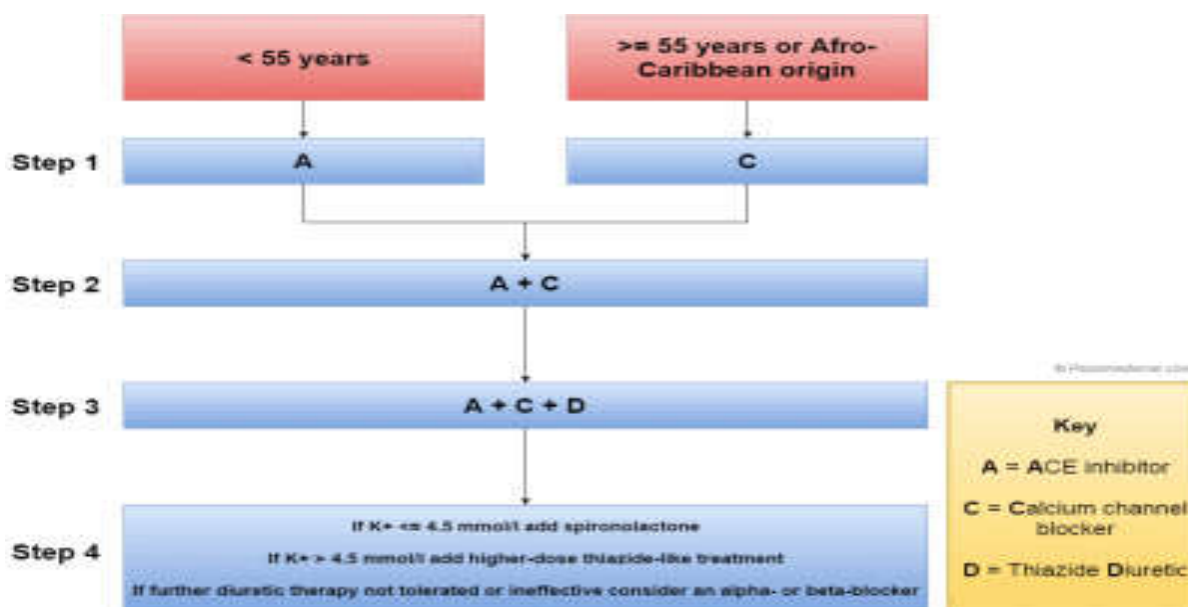
Thiazide diuretics work by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT). Potassium is lost as a result of more sodium reaching the collecting ducts. Thiazide diuretics have a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Common adverse effects

- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, hypercalcaemia
- gout
- impaired glucose tolerance
- impotence

Rare adverse effects

- thrombocytopenia
- agranulocytosis
- photosensitivity rash
- pancreatitis



Flow chart showing the management of hypertension as per current NICE guidelines

Trimethoprim

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.

Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

Adverse effects

- myelosuppression
- transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug

Trinucleotide repeat disorders

Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides. These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation*. In most cases, an increase in the severity of symptoms is also noted

Examples - note dominance of neurological disorders

- Fragile X (CGG)
- Huntington's (CAG)
- myotonic dystrophy (CTG)
- Friedreich's ataxia* (GAA)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- dentatorubral pallidoluysian atrophy

*Friedreich's ataxia is unusual in not demonstrating anticipation

Tumour suppressor genes

Basics

- genes which normally control the cell cycle
- loss of function results in an increased risk of cancer
- both alleles must be mutated before cancer occurs.

Examples

Gene	Associated cancers
p53	Common to many cancers, Li-Fraumeni syndrome
APC	Colorectal cancer
BRCA1	Breast and ovarian cancer
BRCA2	Breast and ovarian cancer
NF1	Neurofibromatosis
Rb	Retinoblastoma
WT1	Wilm's tumour
Multiple tumor suppressor 1 (MTS-1, p16)	Melanoma

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

Turner's syndrome

Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females. It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes. Turner's syndrome is denoted as 45,XO or 45,X

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- bicuspid aortic valve (15%), coarctation of the aorta (5-10%)
- primary amenorrhoea
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- lymphoedema in neonates (especially feet)

There is also an increased incidence of autoimmune disease (especially autoimmune thyroiditis) and Crohn's disease.

Ulnar nerve

Overview

- arises from medial cord of brachial plexus (C8, T1)

Motor to

- medial two lumbricals
- adductor pollicis
- interossei
- hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- flexor carpi ulnaris

Sensory to

- medial 1 1/2 fingers (palmar and dorsal aspects)

Patterns of damage

Damage at wrist

- 'claw hand' - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
- wasting and paralysis of hypothenar muscles
- sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)

Damage at elbow

- as above (however, ulnar paradox - clawing is more severe in distal lesions)
- radial deviation of wrist

Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
Axillary nerve (C5,C6)	Shoulder abduction (deltoid muscle)	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation Results in flattened deltoid
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture Palsy results in wrist drop
Median nerve (C6, C8, T1)	LOAF* muscles Features depend on the site of the lesion: - wrist: paralysis of thenar muscles, opponens pollicis - elbow: loss of pronation of forearm and weak wrist flexion	Palmar aspect of lateral 3½ fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial 1½ fingers	Medial epicondyle fracture Damage may result in a 'claw hand'
Long thoracic nerve (C5-C7)	Serratus anterior		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy Damage results in a winged scapula

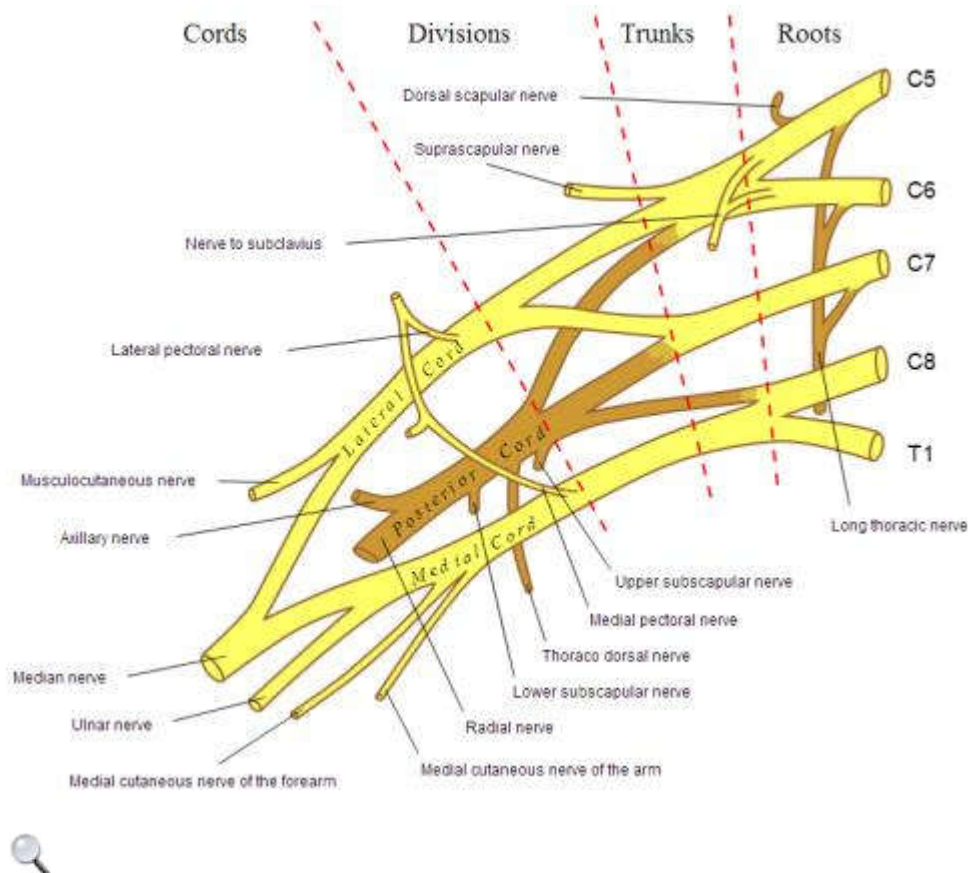


Diagram of the brachial plexus

Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Klumpke injury

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- as above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand
- associated with Horner's syndrome

*LOAF muscles

- Lateral two lumbricals
- Opponens pollicis
- Abductor pollicis brevis
- Flexor pollicis brevis

Valsalva manoeuvre

The Valsalva manoeuvre describes a forced expiration against a closed glottis. This leads to increased intrathoracic pressure which in turn has a number of effects on the cardiovascular system.

Uses

- to terminate an episode of supraventricular tachycardia
- normalizing middle-ear pressures

Stages of the Valsalva manoeuvre

- 1. Increased intrathoracic pressure
- 2. Resultant increase in venous and right atrial pressure reduces venous return
- 3. The reduced preload leads to a fall in the cardiac output (Frank-Starling mechanism)
- 4. When the pressure is released there is a further slight fall in cardiac output due to increased aortic volume
- 5. Return of normal cardiac output

Vitamin C (ascorbic acid)

Vitamin C is a water soluble vitamin.

Functions

- antioxidant
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
- facilitates iron absorption
- cofactor for norepinephrine synthesis

♦Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing

Features vitamin C deficiency

- gingivitis, loose teeth
- poor wound healing
- bleeding from gums, haematuria, epistaxis
- general malaise

External Links

[Merck manual](#)

Useful overview of vitamins

Vitamin D

Vitamin D is a fat soluble vitamin that plays a key role in calcium and phosphate metabolism.

Sources

- vitamin D2 (ergocalciferol): plants
- vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight

Functions

- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

Consequences of vitamin D deficiency:

- rickets: seen in children
- osteomalacia: seen in adults

Vitamin D-resistant rickets

Vitamin D-resistant rickets is a X-linked dominant condition which usually presents in infancy with failure to thrive. It is caused by impaired phosphate reabsorption in the renal tubules

Features

- failure to thrive
- normal serum calcium, low phosphate, elevated alkaline phosphatase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis is made by demonstrating increased urinary phosphate

Management

- high-dose vitamin D supplements
- oral phosphate supplements

Vitamin deficiency

The table below summarises vitamin deficiency states

Vitamin	Chemical name	Deficiency state
A	Retinoids	Night-blindness (nyctalopia)
B1	Thiamine	Beriberi - polyneuropathy, Wernicke-Korsakoff syndrome - heart failure
B3	Niacin	Pellagra - dermatitis - diarrhoea - dementia
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
B9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
C	Ascorbic acid	Scurvy - gingivitis - bleeding
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
E	Tocopherol, tocotrienol	Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
K	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome causes primary immunodeficiency due to a combined B- and T-cell dysfunction. It is inherited in a X-linked recessive fashion and is thought to be caused by mutation in the WASP gene.

Features

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia
- low IgM levels

X-linked dominant

The following conditions are inherited in a X-linked dominant fashion*:

- Alport's syndrome (in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing)
- Rett syndrome
- Vitamin D resistant rickets

*pseudohypoparathyroidism was previously classified as an X-linked dominant condition but has now been shown to be inherited in an autosomal dominant fashion in the majority of cases

X-linked recessive

- In X-linked recessive inheritance only males are affected. An exception to this seen in examinations are patients with Turner's syndrome, who are affected due to only having one X chromosome. X-linked recessive disorders are transmitted by heterozygote females (carriers) and male-to-male transmission is not seen. Affected males can only have unaffected sons and carrier daughters.
- Each male child of a heterozygous female carrier has a 50% chance of being affected whilst each female child of a heterozygous female carrier has a 50% chance of being a carrier.
- The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.

X-linked recessive conditions

The following conditions are inherited in a X-linked recessive fashion:

Androgen insensitivity syndrome
Becker muscular dystrophy
Colour blindness
Duchenne muscular dystrophy
Fabry's disease
G6PD deficiency
Haemophilia A,B
Hunter's disease
Lesch-Nyhan syndrome
Nephrogenic diabetes insipidus
Ocular albinism
Retinitis pigmentosa
Wiskott-Aldrich syndrome

The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:

Chronic granulomatous disease (in > 70%)

External Links

[GMC](#)

GMC guidelines